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ON HEALTH SYSTEMS

I. INTRODUCTION

JOHANNES FRANDSEN

The first germ of a public health service grew out of terror of the great epidemics. Their prevention and combating required a permanent state of readiness that was maintainable solely out of the public purse.

Disease began it all. It was the necessity of treating the sick and the fear of sickness that formed the foundation upon which the health service was built — and it was the physician who, from his knowledge of the cause of disease and the treatment of the sick, formed the demand for funds for treatment and prevention.

This first germ of comprehension of how to fight and prevent disease and to care for health as a common concern grew in country after country at different times and under conditions of growth that varied widely.

The tasks and working conditions of health services are not the same anywhere in the world. Not only do the nature of the diseases and the climates engender differences, but the political and social conditions, as well as the educational standard of the population and its whole cultural status, differ from country to country and contribute equally in making the general picture of the health status and the health work so rich in colour and in the stark contrasts of light and shade.

In countries where the epidemic diseases are not yet under control, the fight against them must necessarily mould the character of the health service.

It is quite another picture where these epidemics are not only under control, but eradicated, where even infectious diseases like TB and VD are firmly under control and receding steadily. Here the sick person, from whom the inspiration to all health care emanates, is no longer the cholera patient; he has been replaced by a highly multiform concept — as multiform and many-sided as a list of diagnoses for the patients admitted to a modern central hospital.

The health legislation, which in such a community must prescribe the scope of the work and provide the economic background for its performance, expands correspondingly. Nowadays, it is no longer simply a matter of preventing infectious diseases but of providing opportunities for the proper and timely treatment of the sick as a whole, of preventing sickness as far as possible and keeping healthy people healthy.

With the preservation of health as a valid section of the health service, a bridge is built between health legislation and that social legislation which besides making the individual secure against the economic sequelae of sickness, has the effect of promoting health by means of relieving social need.

The conditions under which a health service has to work are anything but homogeneous. Its organization and position within the community differ in the various countries, and its working problems are also different.

But we all have the same goal and we need to know one another's circumstances, to exchange experiences to our mutual advantage. None of us has achieved so much that we don't think there is still more to be done.

Physicians are quite familiar with regarding their science and art from an international angle. Scientific congresses and mutual visits on study journeys to universities and hospitals determine this and are a valid link between medical men of the clinic — of the sphere of disease treatment.

From the National Health Service. Director-General: *Johannes Frandsen*.

For physicians who work in other domains of health care, and for non-medical workers in the service of public health, there is the same desire and need for intercourse and collaboration. But the task of international co-operation between the organizations of the health system will not be confined to purely medical problems; they will be just as multilateral as the various tasks of the health services. Congresses, in the ordinary sense, will not suffice; the goal can be reached only by means of a more comprehensive organization than brief gatherings.

The old League of Nations had already worked with no little success to promote international co-operation by setting up a Health Committee, and that idea and that work are now being carried on by WHO along more definite and, in many ways, more effective lines.

Apart from the many great concrete tasks calling for WHO's undivided attention from the very outset, the question of health service organization and administration itself was bound to give rise to discussion and arouse interest.

Under what forms of organization and administration does the work give the best results?

Can we devise general rules that will be of help to all us of despite our mutual differences?

Questions such as these and many others are vividly present among all who work in the service of public health. Hence, it was only natural that even the third WHO assembly resolved to appoint a committee to study the forms of public health administration and try to devise guiding lines for organization and scope.

The committee was able to terminate its work with a most interesting report*), a valuable platform for the further discussion of these questions which are so vitally important to health work.

The report naturally can only be — and is doubtless so regarded by the committee itself — an introduction, an inspiring introduction to future written and oral contributions to the debate on this extensive and many-sided subject, one that will always appear on the agenda when the affairs of health service are to be discussed.

For this more profound discussion of the future, it would be of great value, indeed of almost vital importance, to gather full particulars of the health services of the various countries, with accounts of their organization and administration and accompanied by such comments and observations as may be founded upon and justified by experience and working results. Naturally, that must also include particulars of social legislation apart from the purely health legislation and of social conditions as a whole.

To allow for the evaluation of the efficiency of a health service, the suggestion has been made to collect information on the cost of health work per head of the population. Differences in administrative structure and in budgetary planning, as well as in forms of accounting, however, would make such information so heterogeneous as to be inapplicable as a basis for comparison between the countries.

The efficiency of a health service can be measured and appraised only by its results. On the other hand, good working results need not signify that the organization and the methods employed are the only possible ones for achieving such results. Nevertheless, good results warrant the attribution of such great value to the legislation and organization which have created the scope and the economic conditions for the work, that one ought to take the trouble of becoming acquainted with them.

Outstanding among WHO's many and great objects is the procurement of co-operation among the various countries for the advancement of health work — *inter alia*, and not least, by the exchange of opinions and experiences for the evaluation of means and aims.

One important, indeed imperative basis for such co-operation is a mutual knowledge of the forms of organization and administration under which the health services operate and of their results.

This being so, there is every reason for emphasizing the desirability of inducing as many countries as possible to publish and to circulate as widely as possible reports on their health legislation and the principles embodied in the structure of their organization and administration, as well as on the results achieved, to enable an estimate to be formed of the efficiency of their health services.

Reports of this character should be kept within reasonable compass and free of burdensome details, to which those more interested may have access through other channels.

*) WHO Technical Report Series No. 55.

ANEMIA IN CHRONIC DISEASES OF THE KIDNEYS

By JOHS. GORMSEN and POUL A. GJØRUP

The purpose of the present paper is to try to throw a light upon new theories regarding the origins of nephrogenous anemia.

We shall especially deal with the conditions of the bone marrow, and the intra- and extracorpuscular haemolytic factors determined by means of differential agglutination of erythrocytes — and finally we shall submit some observations made within this field among our own material.

Formerly, the theory prevailed that a toxin formed or retained owing to the renal insufficiency, caused damage to the bone marrow and reduced the production of erythrocytes (1, 4, 7, 29).

Several authors have demonstrated a correlation between the degree of anemia and the amount of one or more substances — urea and creatinine — retained on account of the renal insufficiency (4, 5, 7, 16, 32, 37), and they take this as a proof that a toxin retained, as for instance urea, is responsible for the anemia. Bock & Thedering (4) state that generally an anemia will exist when the serum creatinine rises above 2 mg % or the serum urea is above 70 mg %. Roscoe (31) is of the opinion that a 50 mg % rise in the blood urea is accompanied by a decline in the haemoglobin of 1.8 %. Still the decline in the haemoglobin ceases when the blood urea rises above 250 mg %. In agreement with these results Callen & Limarzi (7) state that no further decline in the haemoglobin occurs in case the NPN (non-protein nitrogen) rises above 100 mg %.

However, recent investigations have shown that anemia may exist in chronic diseases of the kidneys without an absolute renal insufficiency being present, for which reason etiological possibilities other than toxins must be taken into consideration; and furthermore, that the mechanism of origin of the anemia is more complicated than has formerly been presumed, as besides the damage to the bone marrow, increased peripheral destruction of erythrocytes has been demonstrated (3, 8, 12, 13, 18, 23, 24, 26, 28). In advance it would seem likely that the pathogenesis of the anemia should prove diverse in diseases so etiologically different as chronic glomerulonephritis, pyelonephritis and nephrosclerosis, unless the all decisive factor simply is the fact that: the kidneys are injured.

Iron, liver extracts, B_{12}, or folic acid have no effect on the anemia. Cobalt (cobaltous chloride) (33, 36) seems to possess a non-specific stimulating effect on the bone marrow in these diseases. A splenic inhibition on the bone marrow is not probable: Riley Houck has not been able to obtain an improvement of the anemia by splenectomy on nephrectomized dogs. Lack of protein is hardly of any importance, unless specific lack of an amino acid is concerned. Hydremia is a rare feature in chronic diseases of the kidneys and accordingly is not contributing to the low haemoglobin values. Hemorrhages may, in rare cases, be a concurrent cause of the anemia.

THE PERIPHERAL BLOOD PICTURE

Anemias of all degrees are found, but the percentage of haemoglobin seldom goes down below 40, unless hemorrhages supervene.

The anemia is normochromic. Maier (25) and Dacie (10) state that angular especially triangular erythrocytes (in "wet" preparation) are frequently met with in these anemias. Similar triangular cells are also seen in the haemolytic anemias that may accompany malignant tumours and liver diseases, and are held to be caused by some abnormal waste products. Reports state varying numbers of reticulocytes. Those investigators who report evidence of haemolytic anemia generally find a moderate reticulocytosis too, whereas other investigators report normal or even reduced numbers of reticulocytes. The leucocyte figure is often normal; leucocytosis may exist leucopenia is rare. The thrombocyte figure is normal or slightly reduced. The serum iron is generally normal.

CONDITIONS OF THE BONE MARROW

The view has formerly been held that the bone marrow is hypoplastic in cases of nephrogenous anemias (7, 29 (review)), a concept that has been revised in recent years. The erythrogenic system is often hyperplastic. Callen & Limarzi (7) report that among 102 patients they have not seen aplasia, and seldom hypoplasia, and then only in those cases in which the NPN was above 150 mg %. Most patients had hyperplastic bone marrow. Levin & Gregory have examined 24 patients with a mean NPN of 154 mg %, and find in 10 of these patients hyperplasia of the bone marrow. Nor has Sacchetti (34) been able to demonstrate any hypoplasia. He has carried out a study of the rate of growth of the bone marrow in the patients' serum and found both maturation and proliferation of the erythroblast to be retarted. If, however, the bone marrow was placed in normal serum, normal

From the Copenhagen County Hospital, Hellerup, Medical Department F; Head: *F. Wulff*, and Medical Department N; Head: *E. D. Bartels*.

conditions quickly developed. Consequently, a drastic and irreversible change in the maturation of erythroblasts can be ruled out. Thus the erythrogenic system of the bone marrow is, from a morphologic point of view, generally hyperplastic, (and may only in more severe cases of uremia become hypoplastic).

However, there can be no doubt that the bone marrow is functionally deficient, as the peripherally increased haemolysis is not so marked as to be able to account for the anemia alone. It has been proved (9) that the bone marrow in haemolytic anemias from other causes may increase the production of erythrocytes to seven times that of the normal. With an intact bone marrow, anemia should therefore not be suspected, until the length of life of erythrocytes had fallen to one seventh that of the normal, i. e., 18—20 days, and experience seems to lend support to this view. In the nephrogenous anemias the length of life of erythrocytes is seldom reduced below one third to one half that of the normal, from which the conclusion may safely be drawn that functionally the bone marrow is hypoplastic. The causes of this hypofunctioning have not been brought to light. Experiments undertaken by Sacchetti (34) suggest that an inhibition of maturation may be the underlying cause. No conclusive proofs have been established in vivo that an inhibition of maturation or of transmission is involved.

Richet, Alagille & Fournier (30), in 21 patients suffering from acute anuria, have found a specific wastage of the erythroblast around the fifth day up to two months after the occurrence of the anemia. Similar anomalies are absent in chronic uremias, but it is at least conceivable that such disturbances may be present in a mild degree during acute exacerbations of the disease.

However, it seems safe to presume that pathogenic differences exist between the acute and the chronic nephrogenous anemia. The myeloid system of the bone marrow is generally hyperplastic. Perhaps, in this respect, it may be of importance if an infectious element comes into play (pyelonephritis). The megacaryocytic conditions are most likely normal, while, as a rule, the number of reticulum cells and plasma cells has been increased.

HAEMOLYTIC FACTORS

"Intracorpuscular factors".

Considerable interest is attached to the point whether defective erythrocytes of a reduced length of life are being formed in the bone marrow, similar to what is known in the case of, for instance, congenital haemolytic anemia, sickle cell anemia, nocturnal haemoglobinuria and other diseases. In that case the primary cause is deemed to be the action on the bone marrow, while the result is manifested "peripherally", where the defective erythrocytes are undergoing an abnormally rapid destruction. Transfusion tests have borne out this theory. (See below).

"Extracorpuscular factors".

Besides the above-mentioned action on the bone marrow and the increased haemolysis owing to an inherent defect of the erythrocytes, another factor of importance will be mentioned: The extracorpuscular haemolytic factors, i. e., the destructive agents outside the erythrocytic membrane. There will often be a coincidence of the effect of both the elements productive of haemolysis, as the primarily damaged erythrocytes will prove more susceptible to the extracorpuscular destructive agents. Conclusive proof of the presence of extracorpuscular haemolytic agents has been demonstrated by survival tests of erythrocytes. (See below).

As to actual mechanism of haemolysis, theories are still mere guesswork. Disturbances in electrolytic conditions, acidosis, any shifts in the balance of haemolytic and anti-haemolytic factors, abnormal protein conditions, (also reflected in changes in the electrophoretic picture) may all induce changes of membranes.

An infectious element may play a part. The reticulo-endothelial system may be hyperfunctioning. In some few cases immune-haemolytic factors become actual (positive Coomb). On autopsy of 21 patients, who died from renal insufficiency with hypertension and anemia, (most of whom had not not received blood transfusions) Muirhead (10, 18) found erythrophagocytosis and haemosiderosis in one or more reticulo-endothelial structures in 20 of these patients. On section of 7 patients with hypertension and renal insufficiency, but without anemia, the same anomalies were encountered in 3 patients.

In experiences with bilateral nephrectomy on animals, similar changes were found. Generally the haemolysis in chronic nephritis can not be demonstrated by means of the ordinary methods: the serum bilirubin is normal, as is the excretion of stercobilin in faeces. The osmotic resistance varies within normal limits.

Survival time of erythrocytes.

As mentioned above, the haemolytic element of the chronic anemias of the kidneys can not be demonstrated by ordinary methods. Valuable information, however, is obtainable by determinations of the erythrocytic survival time (review: 11). In order to be able to prove the existence of intracorpuscular haemolytic elements, the defective erythrocytes are transfused to a normal person. In order to be able to prove the existence of extracorpuscular elements, normal erythrocytes are transfused to the patient.

By this method the organism is assumed to deal with the erythrocytes of donor and recipient in a similar manner.

The method was originally introduced by Ashby (2) and is adopted by one of us (Go.) in modification of the method of Mollison and Dacie. In order to be able to retrieve the erythrocytes, it becomes necessary to mark them. This can be done by means of radioactive iron or better chrome, or easier still by transfusing to the patient blood cells of a different type (preferably Type O, or if the patient's blood is of Type O, then another MN group.). The determination of the surviving erythrocytes is accomplished in the first case by radioactive measurement and in the second case by differential agglutination or haemolysis. To blood drawn from the patient is added that serum which agglutinates the patient's erythrocytes, whereafter the transfused blood cells remain. These are now counted in a counting chamber and the number of erythrocytes may be stated, for instance as a percentage of the number found twenty-four hours after transfusion. (Normally any shifts in the volume of cells will be equalized in twenty-four hours).

The differential agglutination method has its faults. A homogenous potent serum must be used, and the countings are subject to the usual sources of error.

If in a system of co-ordinates, the number of days are fixed as abscissa, and as ordinate, the number of surviving erythrocytes, stated in percentage of the original number, and determined, for instance, by weekly counts, an Ashby curve will appear, which may take various principal courses. If a transfusion of normal blood has been given to a normal human, the curve will run rectilineally obliquely downwards from a point in the ordinate, to intercept the abscissa in about 120 days: normally the potential duration of life of the erythrocytes. The daily destruction of erythrocytes takes place according to age, a certain percentage being destructed daily: the curve runs a rectilineal course. A different possibility (confer Fig. 1.), which is pathologic, is the shortened rectilineal curve. The daily destruction, also in this case, takes place according to age, but a greater amount of erythrocytes are being destructed daily. Finally we shall mention the curve typical of the extracorpuscular haemolysis (random destruction). In this case, the destruction takes place partly according to age and partly owing to haemolytic elements outside the erythrocytes. The curve runs an exponential course. Te number of erythrocytes surviving after a period of about sixty days will be reduced, whereas the potential life span need not to be reduced, even if this is often the case. In some cases the haemolysis is so pronounced that the destruction of erythrocytes according to age is of no importance. A reduced length of life, in respect to erythrocytes taken from a patient and transferred to a normal person, is met with, for instance, in congenital hemolytic anemia, nocturnal haemoglobinuria (Marchiafava) elliptocystosis, sickle cell anemia, thalassemia. *Random* destruction is encountered in acquired haemolytic anemia, leukemia, various lymphatic diseases, in certain forms of cancer, liver diseases, in renal insufficiency and presumably in pernicious anemia. We shall now deal in some detail with the survival time of the erythrocytes (the s. t.) in chronic diseases of the kidneys. By transfusion of erythrocytes from patient to normal person, a reduced length of life of the erythrocytes has been demonstrated, indicating that the erythrocytes developed are being defective (intracorpuscular factors). (6).

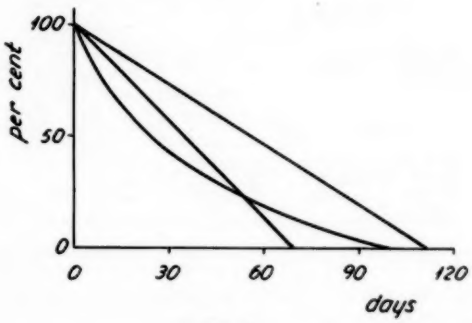

Fig. 1.
Survival time of erythrocytes, various possibilities. (cf. text).

By far the majority of the transfusion tests are from normal person to patient. Bock (3) and co-workers have undertaken an examination of 14 patients suffering from renal insufficiency and have encountered all three types of curves as shown in Fig. 1, the normal one, the shortened rectilineal curve, and the exponential curve. One-half of the patients examined showed normal s. t., the shortest being approximately 55 days.

Low haemoglobin percent was accompanied by short s. t., but they were unable to demonstrate any correlation between s. t. and type of curve on the one hand, and renal function, blood pressure, duration of disease or perhaps inflammatory condition on the other. Emerson & Burrows (13) have reported 4 cases of marked anemia and azotemia. The s. t. was reduced to one-third that of normal. However, these investigators state an inhibition of the bone marrow as being the primary cause of the disease. Loge, Lange & Moore make a distinction between patients with chronic renal insufficiency with a relatively stationary anemia and normal s. t., and patients with chronic glomerulonephritis and pronounced azotemia, as the latter during periods of acute exacerbations of the anemia reveal a reduced s. t. They draw the conclusion that the progression of the anemia is due to deficient function of the bone marrow concurrent with extracorpuscular haemolysis. Reports by Chaplin & Mollison (8) confirm this theory: in case of rapid deterioration of the renal disease,

Table 1.

Patient No.	Diagnose	Endogenous creatinin clearance	Icterus index	Bilirubin mg/100ml	Osmot. resist.	Coomb test	Colour index	Serum iron mg/100ml	Leucocytes	Electrophoresis	Bone marrow
I	Pyelonephritis chron.	12 ml/min.	10	0.35	slightly decreased	÷	1	0,149	normal	Total protein 7.4 %. Gammaglobulin decreased, other fractions slightly increased	Erythropoiesis slightly hyperplastic left-hand deviated. Myelocyte system hyperplastic, left-hand deviated. Megacaryocytes normal. Plasma- and reticulum cells normal.
II	Pyelonephritis chron.	10 ml/min.	3		normal	÷	1	0,110	left-hand deviation	normal	Erythropoiesis slightly hyperplastic left-hand deviated. Myelocyte system hyperplastic, left-hand deviated. Megacaryocytes normal. Plasma cells increased.
III	Glomerulonephritis chron.	8—10 ml/min.	3	0.26	normal	doubtful positive	ca. 1	0,190	normal	Total protein 6.3 %. Gammaglobulin decreased. Alfa 2 globulin slightly increased	Erythropoiesis hyperplastic. Myelocyte system hyperplastic, left-hand deviated. Megacarycoytes, plasmacells and reticulum cells normal.
IV	Pyelonephritis chron. Pyonephrosis	ca. 5 ml/min.	2	0.26	normal	÷	1	0,223	left-hand deviation	Total protein 6.7 %. Albumin markedly decreased. Alfaglobulines normal. Gammaglobulines markedly increased	Erythropoiesis sparsely represented. Myelocyte system hyperplastic, left-hand deviated, dominating the picture. Megacaryocytes: some. Plasma and reticulum cells increased.

they found the s. t. in 3 patients reduced to approximately 16, 32 and 59 days.

In patients suffering from a stationary chronic renal insufficiency, they reported a normal s. t.

Muirhead and co-workers (26, 27, 28), as also Loge and co-workers (24), in experiments on animals (nephrectomy or ligation of the ureter), have emphasized the same causes of the anemia:

Partly a hypofunctioning bone marrow and partly an increased peripheral extracorpuscular haemolysis. In these experiments, however, rapidly developed anemias are concerned and the conditions of such anemias can only to some extent be compared to those of the chronic renal anemias.

MATERIAL

We have examined four patients: I. A woman aged 61 suffering from chronic pyelonephritis, with normal blood pressure. II. A woman aged 57 suffering from chronic pyelonephritis, with normal blood pressure. III. A man aged 56 suffering from chronic glomerulonephritis, and with a slightly elevated blood pressure. IV. A woman aged 43 suffering from chronic pyelonephritis and right-sided pyonephrosis, with normal blood pressure.

The patients have been under observation from three to nine months including regular examinations of blood status and renal function. By transfusions of normal blood to the patient, the s. t. has been determined one or more times in all patients. The treatment usually employed in chronic renal diseases has been applied to all four patients, including blood transfusions. Patient No. IV has been further treated with haemodialysis. The patients I, II and III have for months been treated with 50 mg of cortisone daily without any untoward side effects having appeared, especially no elevated blood pressure. In all three cases the general well-being of the patients improved during cortisone treatment. Patient No. III, who had been incapacitated for work six months previous to treatment, was again able to attend to his work. Our impression is that cortisone exercised a beneficial effect on the anemia, enabling the patients to do without transfusions for lengthy periods of time. However, no safe conclusions can be drawn in this respect until a more extensive control material is available. Results are stated in Tables I and II, as well as in

Table 2.

Patient No.	Haemoglobin %, "level"	Erythrocyte survival days	Ashby curve	Serum creatinin mg/100 ml	Blood urea mg/100 ml	Erythropoiesis in bone marrow	Reticulocytosis
I	70	> 100	straight	3—4	100	slight hyperplasia	÷
II	60—70	∧ 100	straight	ca. 5	ca. 100	slight hyperplasia	÷
III	50—65	1)30 - 2)40 - 3)45	exponent	5—6	ca. 200	hyperplasia	+
IV	40—50	very short	exponent?	ca. 10	250—300	hypoplasa	÷

Figs. 2, 3, 4, and 5. It appears from Table I that: the renal function, as measured by 24-hour endogenous creatinine-clearance was heavily reduced in all cases, ranging from 12 to 15 per cent that of normal, and the power of concentration was suspended. Ordinary tests of haemolysis were negative. Coomb-test was negative in three cases and doubtful positive in one case. Electrophoretic results seem to be varying. The erythrocytic system of the bone marrow is hyperplastic in three patients, while in patient No. IV it is hypoplastic. This patient had the most insufficient renal function and a blood urea varying between 250 and 300 mg %. The myeloid system was in all cases hyperplastic and shifted to the left, whereas circulating granulocytes showed a shift to the left in only two of the patients.

In Figs. 2, 3, 4, 5 are stated the results of continued determinations of the percentage of haemoglobin, the number of leucocytes, thrombocytes and reticulocytes, blood urea and the serum creatin values, and treatment with transfusions and cortisone, as also the periods during which survival time of erythrocytes has been determined (stating the length of the s. t.). As to the s. t. patients Nos. I and II (Figs. 2 and 3) displayed a retilineal type of curve (Fig. 1); in both patients the s. t. was approximately 100 days, i. e., slightly reduced, still not necessarily abnormal. In patient No. III (Fig. 4) the s. t. was

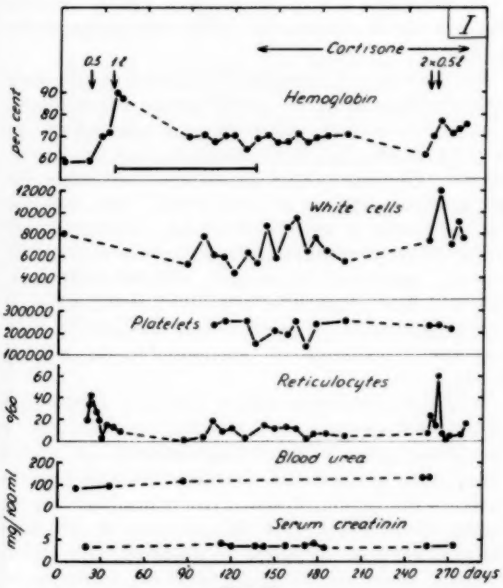

Fig. 2.

Patient No. I. Results of continuous determinations of haemoglobin, leucocytes, thrombocytes, reticulocytes, blood urea, and serum creatinin. The arrows indicate the blood administered. The straight line below the haemoglobin curve indicates the life span of the erythrocytes.

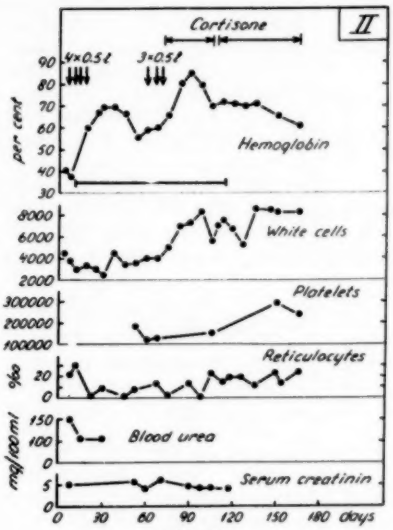

Fig. 3.

Patient No. II. Legend as in Fig. 2.

determined three times, and all three times the Ashby curve ran an exponential course. At the first determination the survival time was about 30 days only. This was reflected in a poor clinic picture with a rapidly falling percentage of haemoglobin. At the next determination — at this time the patient was undergoing a cortisone treatment — the s. t. was about 40 days, with a but slowly

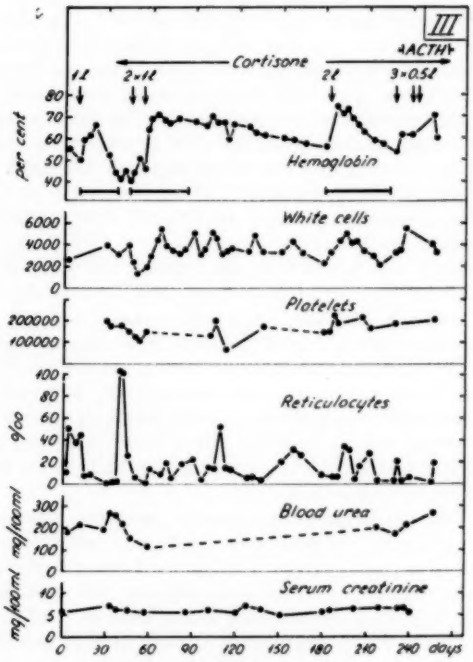

Fig. 4.

Patient No. III. Legend as in Fig. 2.

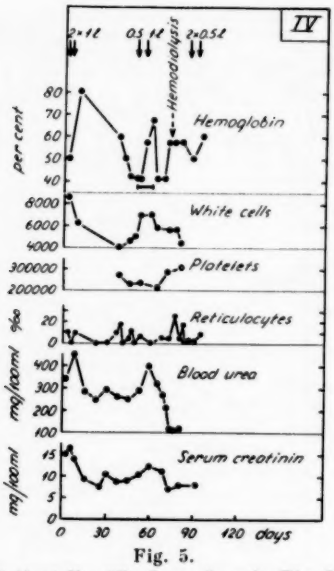

Fig. 5.
Patient No. IV. Legend as in Fig. 2.

declining Hb. and a much better general well-being. With the third determination the s. t. was about 45 days. In patient No. IV (Fig. 5), in respect to whom determination of the survival period of erythrocytes was made at a time when the clinical condition was very poor, almost none of the red cells transfused were left 12—15 days after the transfusion. At the time epistaxis occurred and the determinations were abandoned. This patient's Ashby curve is short and precipitous and nothing certain can be said of the type. We think that the curve is an example of an exponential curve taking a very precipitous course.

In Table 2 are gathered those relevant factors most necessary for a conclusion. The table states the haemoglobin level. This is based on an approximate estimate and represents the fluctuating levels of the percentage of haemoglobin, particularly through lengthy periods of time without transfusion treatment.

Since the material is so limited, no safe conclusions can be drawn from the results stated in Table 2. Still the table does reveal a tendency: the haemoglobin level declines in harmony with declining renal function. At failing renal function, the Ashby curves become exponential, indicating a haemolytic condition, and this haemolysis is the stronger, the more reduced the renal function is, and especially during acute exacerbations of the patient's condition.

The erythrocytic system of the bone marrow is generally hyperplastic, and was only hypoplastic in the patient with poorest renal function and a blood urea varying between 250 and 300 mg % (in agreement with the results of C a l l e n & L i m a r z i). Reticulosis is only seen in patient No. III, in whom the determination of s. t. displayed strong evidence of haemolysis. In patient No. IV a pronounced haemolysis was manifest too, whereas there were no signs of reticulocytosis, probably because the bone marrow, which from a morphological point of view was hypoplastic, was unable to induce a rise of reticulocytes. The patients Nos. I and II displayed no reticulocytosis, which was reflected in the determinations of the s. t., which yielded no certain signs of a haemolytic condition.

During the periods when determinations of the survival time of erythrocytes were being made, the patients Nos. I and II contracted a slight catarrhal infection. In patient No. I this infection did not give rise to any disturbances in the Hb. or in the Ashby curve, while in patient No. II the infection was accompanied by a decline of 10—15 in the Hb., but no changes in the Ashby curve. Presumably the declining percentage of haemoglobin must have been due to a response by the bone marrow.

SUMMARY AND CONCLUSIONS

In chronic renal diseases anemia is a classic symptom.

In recent years some light has been thrown on the pathogenesis of this anemia. Three factors at least seem to be of significance:

1) An unknown affection of the function of the bone marrow, different from:

2) A production of defective erythrocytes, i. e., erythrocytes that are being easily haemolysed and accordingly possessing a shorter length of life — in normal blood too. (The intracorpuscular factors).

3) Strongly acting haemolytic agents outside the red blood corpuscles. (The extracorpuscular factors).

On the basis of these observations the following working theory, partly confirmed in experiments, can be raised: in mild cases, even before an anemia exists, the bone marrow may be hyperplastic. The haemolytic agents (perhaps only the intracorpuscular ones) are active, but still the bone marrow is able to make up for accelerated destruction of erythrocytes. In severe cases with anemia: increased haemolysis and the bone marrow are now so affected that even if the latter is still hyperplastic, it is no longer capable of raising the percentage of haemoglobin to normal levels.

A balance between production and destruction of erythrocytes is now appearing, as reflected in the lower percentage of haemoglobin. In severe cases with pronounced anemia: stronger haemolysis — the action of the extracorpuscular agents seems to intensify with the increase of non-protein-nitrogen in the blood — together with an increased stress on the bone marrow, perhaps resulting in hypoplasia. The failure of the bone marrow may be due partly to functional exhaustion, but may also be due to some deficiency, or a toxic action by some product retained owing to the renal insufficiency, involving a primary inhibition of maturation and transmission. The

percentage of haemoglobin will always be dependent on the balance existing between haemolytic agents and the conditions of the bone marrow. In case this state of balance is disturbed, conditions will facilitate increased anemia. This balance may be disturbed by exacerbations of the primary disease (increasing uremia), but also by other circumstances, e. g., intercurrent infections.

The authors have examined four patients, suffering from chronic renal diseases and uremia of varying degree of severity, especially with regard to determination of the survival time of erythrocytes in transfusions of normal blood to patient, and have arrived at the following conclusions:

1) The degree of severity of the anemia was found to be dependent on renal function, but no rectilineal relation existed between the percentage of haemoglobin and the serum creatinin or blood urea.

2) An abnormally strong haemolysis owing to extracorpuscular agents was a concurrent cause of the anemia in the two patients with poorest renal function. The haemolysis increased with declining renal function.

3) The erythrocytic system of the bone marrow was hyperfunctioning in three patients and hypofunctioning in the patient with the most deficient renal function. 24-hour creatinine-clearance was approximately 5 ml/min.

References:

1) *Alder, A.:* Deutsche Med. Wochschr. 1952, *17:* 536.
2) *Ashby, W.:* J. Exp. Med. 1919, *29:* 267.
3) *Bock, H. E., H. Bøttner* and *B. Schlegel:* Z. ges. exp. Med. 1952, *118:* 459.
4) *Bock, H. E.* and *F. Thedering:* Deutsche Arch. Klin. Med. 1952, *199:* 30.
5) *Brown, G. E.* and *G. M. Roth:* Arch. Int. Med. 1922, *817:* 840.
6) *Bøttner, H.* und *B. Schlegel:* Klin. Med. Woch. 1952, *30:* 178.
7) *Callen, I. R.* and *L. R. Limarzi:* Am. J. Clin. Path. 1950, *20:* 3.
8) *Chaplin, H. J.* and *P. L. Mollison:* Clin. Sci. 1953, *12:* 351.
9) *Crosby, W. H.* and *J. H. Akeroyd:* Acta Hæmat. 1953, *9:* 65.
10) *Dacie, J. V.:* The Hæmolytic Anæmias, Churchill Ltd. 1954.
11) *Eadie, G. S.* and *J. W. Brown:* Blood, 1953, *VIII:* 1110.
12) *Emerson, C. R.:* Blood 1948, *3:* 363.
13) *Emerson, C. R.* and *B. A. Burrows:* J. Clin. Invest. 1949, *28:* 779.
14) *Faarup, C.* and *Søeborg Ohlsen:* Nord. Med. 1941, *11:* 2680.
15) *Gardner, F. H.:* J. Lab. Clin. Med. 1953, *41:* 56.
16) *Grollman, A., L. B. Turner* and *J. A. McLean:* Arch. Int. Med. 1954, *87:* 379.
17) *Harris, A. W.* and *J. G. Gibson:* J. Clin. Invest. 1939, *18:* 527.
18) *Hensley, W. J.:* Aust. Ann. Med. 1952, *1:* 180.
19) *Houck, C. Riley:* Am. J. Phys. 1954, *177:* 531.
20) *Hurley, T. H.* and *R. Weisman:* J. Clin. Invest. 1954, *33:* 835.
21) *Leitner, S. J.:* Bone Marrow Biopsy, London, 1949.
22) *Levin, W. C., L. Gregory, H. Tsai* and *R. Gregory:* J. Lab. Clin. Med. 1950, *36:* 954.
23) *Levin, W. C.* and *L. Gregory:* Southern Med. J. 1952, *45:* 121.
24) *Loge, J. P., R. D. Lange* and *C. V. Moore:* J. Clin. Invest 1950, *29:* 830.
25) *Maier, C.:* Hæmolyse und hæmolytische Krankheiten. Bern 1950.
26) *Muirhead, E. E., J. Jones* and *A. Grollman:* J. Lab. Clin. Med. 1952, *39:* 505.
27) *Muirhead, E. E., F. Jones, J. D. Stirman* and *W. D. Lesch:* Am. J. Phys. 1953, *173:* 371.
28) *Muirhead, E. E.* and *W. F. Shields:* Arch. Int. Med. 1952, *40:* 307.
29) *Nordenson, N. G.:* Folia Hæmat. 1938, *59:* 1.
30) *Richet, G., D. Alagille* and *E. Fournier:* Presse Med. 1954, *62:* 50.
31) *Roscoe, M. H.:* Lancet 1952, *I:* 444.
32) *Roscoe, M. H.:* Quart. J. Med. 1950, *19:* 161.
33) *Robinsen, J. C., G. W. James* and *R. M. Kark:* New Eng. J. Med. 1949, *240:* 749.
34) *Sacchetti, C.:* Acta Hæmat. 1953, *IX:* 97.
35) *Schiødt, E.:* Acta Med. Scand. 1938, *95:* 49.
36) *Seaman, A. J.* and *R. D. Koler:* Acta Hæmat. 1953, *9:* 153.
37) *Townsend, S. R., E. Massie* and *R. H. Lyons:* Am. J. Med. Sci. 1937, *194:* 636.

IRREGULAR BLOOD-GROUP ANTIBODIES

INCIDENCE AND CLINICAL SIGNIFICANCE

By FLEMMING KISSMEYER-NIELSEN[1]), KIRSTEN BASTRUP-MADSEN and AKSEL STENDERUP[1])

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A blood-group antibody must be defined as an antibody which gives specific reactions with red blood cells containing the corresponding blood-group antigen. The antigen-antibody reaction usually manifests itself by agglutination of the blood cells, but sometimes — in the presence of complement — by haemolysis. The blood-group antibodies may be classified in several different ways.

A. *Regular blood-group antibodies.* — Anti-A and anti-B, i. e., antibodies with an effect on the first known blood-group antigens designated in the well-known way as A and B.

B. *Irregular blood-group antibodies.* — All blood-group antibodies other than anti-A and anti-B. At the present time numerous blood-group antibodies are known (see Table 1).

Most irregular antibodies are found in a very limited number of individuals, whose sera differ from "normal" sera in that these antibodies are present.

We may also speak of natural or spontaneous antibodies, which occur without demonstrable antigenic stimulation, in contrast to immune blood-group antibodies, which occur after stimulation with the corresponding antigen, usually during pregnancy or after transfusion. Anti-A and anti-B are typical examples of spontaneous antibodies, but may also be a mixture of spontaneous and immune antibodies. Most, but not all, irregular antibodies are of the immune type.

Furthermore, the blood-group antibodies may be divided according to the more or less special methods which are used in the tests for their reactions with the corresponding blood-group antigen or factor. Thus, we speak of:

A. *Complete blood-group antibodies,* which are characterized by being capable of agglutinating blood cells suspended in physiological saline.

B. *Incomplete blood-group antibodies,* which cannot agglutinate blood cells suspended in saline. Special methods are required for the recognition of these incomplete antibodies. Some incomplete antibodies will agglutinate blood cells if they are suspended in viscid media instead of saline (e. g., in 20 per cent bovine albumin or dextran). Other incomplete antibodies are most readily recognized by Coombs' technique or by enzyme treatment of the blood cells (trypsin or papain).

C. *"Warm" or "cold" antibodies* according to the optimum temperature for the action of the antibodies.

During the last 15 years, developments in immunohaematology have occurred with explosive force, and several new blood-group systems have been discovered. The present status of our knowledge appears from the survey given in Table 1. The table is not claimed to be complete, e. g., the so-called "private" blood-group systems and the rarer A and Rh sub-groups are left out. In the last two columns, attempts have been made to give a rough outline of the clinical significance of the individual blood-group antibodies.

It is of considerable interest to know the incidence of irregular antibodies among a mixed hospital population, since it will then be possible to draw conclusions concerning their significance in daily transfusion work and in pregnancy.

Since December, 1953, we have investigated sera from all blood specimens received at the Institute of General Pathology for their possible content of irregular antibodies. The investigations comprise a total of approximately 17,000 specimens from patients and normal subjects.

MATERIAL

The material consists of 17,011 blood specimens from various hospitals in Jutland. The majority of the specimens are from the surgical departments of these hospitals, but a fairly large proportion originates from the obstetrical gynaecological departments of the State Maternity Hospital for Jutland and from the Blood Bank of Aarhus Municipal Hospital. The distribution appears from Table 2.

The material is rather heterogenous in that the specimens from the Blood Bank and the State Maternity Hospital differ from the remaining material. The specimens from the Blood Bank originate from healthy donors who had usually not received transfusions. As expected, we did not find a large number of antibodies in this part of the material.

Approximately one-seventh of the specimens are from the State Maternity Hospital for Jutland.

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Table 1.

Brief survey of the most important blood-group systems and their clinical significance. Clinically, ((+)) indicates extremely slight importance, (+) very slight importance, + some importance, ++ fairly great importance, and +++ great importance. A question mark indicates that clinical significance of the blood-group antibody concerned is unknown.

Blood-group system	Blood-group antigens which may be determined with the corresponding antibodies		Known blood-group antibodies	May give transfusion reactions	May give haemolytic disease of the newborn
ABO	A_1, A_2, B,	Regular antibodies	(anti-A_2) anti-A (anti-A_1)	+++	+
			anti-B	+++	+
MNS	M, N, S, s		anti-M	+	?
			anti-N	(+)	?
			anti-S	(+)	(+)
			anti-s	?	((+))
P	P (p)		anti-P	(+)	?
Rhesus..	D, C, E, c, e, f, d		anti-D	+++	+++
			anti-C	+	+
			anti-E	+	+
			anti-c	(+)	(+)
			anti-e	(+)	?
			anti-f	?	?
			anti-d	?	?
Lutheran.	Lu^a, (Lu^b)	Irregular antibodies.	anti-Lu^a	?	?
Kell.....	K, k		anti-K	++	+
			anti-k	?	((+))
Lewis....	Le^a, Le^b		anti-Le^a	+	?
			anti-Le^b	?	?
Duffy....	Fy^a, Fy^b		anti-Fy^a	+	?
			anti-Fy^b	?	?
Kidd	Jk^a, Jk^b		anti-Jk^a	(+)	?
			anti-Jk^b	(+)	?
Jay.....	Tj^a, (Tj^b)		anti-Tj^a	(+)	(+)

The majority of these specimens originate from pregnant women and at that a selected group, since the State Maternity Hospital is the centre for the treatment of Rh-immunized gravidae from Central Jutland. A very high incidence of antibodies must therefore be expected in this part of the material. In the State Maternity Hospital the antibody titre of the immunized patients is determined several times during pregnancy, usually 3—4 times. In the figures given for antibodies these specimens are included only once, but all the specimens received figure in the total number of blood specimens, so that the actual incidence of antibodies is somewhat higher than stated.

The specimens from the remaining hospitals originate partly from patients and partly from donors. Unfortunately, it is impossible to state the percentile distribution of donors and patients. Some of the specimens are "repeaters", i. e., samples from the same patient or donor submitted twice or several times. We are unable to state the exact number of such repetitions, but at a rough estimate they represent about 8 per cent of the specimens submitted. The actual incidence of antibodies in this part of the material will therefore be about 8 per cent higher than stated.

METHODS

The ABO group and Rh:D group were determined on nearly all the specimens. Some of the specimens from Aarhus County Hospital and from the Surgical Department of Aarhus Municipal Hospital form an exception in that the ABO group and Rh:D group had been determined in the hospitals, while only the sera were submitted for screening for antibodies. This applies to a total of 1,235 specimens.

All the sera of the specimens were studied for irregular antibodies by means of a screening test. By this screening we test the inactivated sera for

antibodies, using blood cells from three different, carefully selected persons of group O, whose antigens cover most of the blood-group spectrum.

In the screening test we use both trypsin-treated red cells and blood cells suspended in 20 per cent albumin. During almost the entire period of investigation we have used test cells with the following antigenic structure:

No. 1. O, CDe/cDE, MNS, p/p, Le (a—b+), K+, Fy (a—), Jk (a—).
No. 2. O, CDe/cDE, MS, P, Le (a+b—), K—.
No. 3. O, cde/cde, MNs, P, Le (a—b+), K—, Fy (a—), Jk (a+), Lu (a—).

A 5 per cent suspension of test cells No. 1 in 20 per cent bovine albumin and 2.5 per cent suspensions of trypsin-modified test cells Nos. 2 and 3 in saline are prepared. Of the serum which is to be screened for antibodies, two, one, and one drop are placed in three separate test tubes. To the first tube one drop of suspension No. 1 is added, and to the second and third tubes two drops of the suspensions Nos. 2 and 3, respectively. All three tubes are incubated at 37° C. for about 2 hours and read macroscopically after gentle shaking. A minority of the specimens (app. 1,200) have been screened for irregular antibodies also at room temperature.

From the agglutination in the three tubes the type of antibody present, if any, may be roughly estimated. The final identification is performed by the usual methods, using a large panel of red blood cells with known blood-group antigens.

Table 2.

Distribution of the 17,011 blood specimens received from Dec. 3, 1953. to Dec. 31, 1954. The last two columns show the frequency of sera containing irregular blood-group antibodies.

Hospital or department	No. of specimens	No. of sera containing antibodies	Percentage
State Maternity Hospital for Jutland	2,660	75	2.82
Aarhus Municipal Hospital:			
Blood Bank	2,386	8	0.34
Dept. G (Neurosurgery)	1,241	9	0.73
Dept. D (Radium Centre for Jutland)	739	7	0.95
Viborg County Hospital	2,318	28	1.21
Aarhus County Hospital	1,387	18	1 30
Kjellerup County Hospital	1,036	10	0.97
Holstebro County Hospital	796	11	1.38
Grenaa County Hospital	688	10	1.45
Other hospitals	3,760	41	1.09
Total	17,011	217	1.28

RESULTS

The results of our investigations are shown in Table 2. Of the approximately 17,000 sera, a total of 217, or 1.28 per cent, contained one or, on rare occasions several irregular antibodies.

The 217 sera contained a total of 219 different irregular antibodies. The distribution appears from Table 3. It should be noted that in this survey a combination of two or three different Rh-antibodies is counted as one irregular antibody.

It appears from the table that 121 Rh antibodies or combinations of different Rh antibodies were disclosed. It appeared that about two-thirds of these antibodies were pure anti-D, and slightly less than one-third a combination of anti-D and one or more other Rh antibodies. Thus, anti-D was present in about 97 per cent of all sera containing Rh antibodies. These figures are in good agreement with similar investigations from Great Britain (5).

DISCUSSION

The material presented shows that the fairly simple technique used in this study revealed a large number of irregular antibodies in sera from a mixed material consisting of patients, donors and pregnant women. The incidence of irregular antibodies disclosed is higher than in other materials. Table 4 shows the results of the present investigation compared with those of similar investigations performed by other authors.

Table 3.

Survey of 217 sera containing 219 irregular antibodies disclosed among 17,011 specimens received from Dec. 3, 1953, to Dec. 31, 1954.

Antibody	No. of irregular antibodies	Percentage of all irregular antibodies	Percentage of Rh-antibodies
anti-D	82		67.8
- D+C	31		25.6
- D+E	1	55.3	0.8
- C+D+E	3		2.5
- C	1		0.8
- E	3		2.5
anti-Le^a	57	26.0	
- Le^b	1	0.5	
- P	26	11.9	
- K	8	3.7	
- M	2	0.9	
- S	1	0.5	
- Fy^a	1	0.5	
Unknown	2*)	0.9	
Total	219		

*) One of these unknown antibodies proved to be a previously unknown antibody, which has been designated as anti-Chr^a. This antibody will be discussed in detail elsewhere. (2).

Table 4.
Incidence of irregular blood-group antibodies in various materials.

Author	Vogel (7)	Grove-Rasmussen (1)	Present material
Number of specimens examined	56,000	20,000	17,011
anti-D.....	95	55	82
- D+C.....	20	24	31
- D+E		1	1
- D+C+E .		3	3
- C.....		2	1
- C^w	1		
- E.....	33	15	3
- c	4	2	
anti-K.....	12	29	8
- Fy^a	2	4	1
- Jk^a	1	1	
- M.....	2		2
- S.....	2		1
- Le^a	9	12	57
- Le^b	12	10	1
- Lu^a	1		
- P.....	6	5	26
Unknown	9		2
Total	209*)	163	219

*) Vogel found other haemagglutinins including anti-A_1(7), anti-O(5), high-titre cold agglutinins (5) and incomplete panagglutinins in acquired haemolytic anaemia (18). These agglutinins have not been included because such agglutinins were excluded from the last two materials.

The discrepancies between the results may be caused by methodological variations and differences in the materials. Anti-E and anti-Kell antibodies were more frequent in Grove-Rasmussen's material. The explanation may be that the patients in his material had received more transfusions than ours. The frequency of anti-E is also high in Vogel's material, and he states that 16 of these antibodies were from patients with haemolytic anaemia, and these patients are often multitransfused and are apt to produce irregular blood-group antibodies by iso-immunization. The large number of anti-Le^a in the present material, which is a noteworthy feature, may be caused by the antigenic structure of our test cells. Both our A_1 test cells used in the serum control for the ABO group and one of our trypsinized red cells used by the antibody screening have been Le (a+) during the whole investigation. The fairly large number of anti-P antibodies in our material may be explained in the same way. Naturally, variations in the antigenic structure of the test cells used by the various authors may account for some of the discrepancies. The large number of anti-D and combinations between this and other Rh antibodies in our material is caused by the relatively large number of blood specimens received from the State Maternity Hospital (Table 2). This problem will be discussed in greater detail below. Levine et al. (3) found 98 irregular antibodies other than anti-D within the space of 12 months (number of specimens investigated unknown). Their material was selected and does not allow for any conclusions as to the incidence of irregular antibodies in unselected material (4).

WHAT ARE THE CONSEQUENCES OF THESE RESULTS IN CLINICAL PRACTICE?

Before any conclusions can be drawn, it is necessary to consider the material and methods used in the investigation in some detail.

The incidence of antibodies in series consisting entirely of patients (-donors) must necessarily be higher than the percentages stated in Table 2, because this table also includes donors who have a relatively low frequency of antibodies (0.34 % in the donors from the blood bank).

Other factors which increase the actual incidence of antibodies are mentioned in the section on the material.

As far as the methods are concerned, it cannot be expected that the screening of the sera should be capable of disclosing every blood-group antibody present. In the first place, it is not possible to cover the entire range of blood-group antigens with blood cells from only three persons. Secondly, Coombs' indirect test, which is presumably the only serological procedure capable of revealing the anti-Fy^a antibody, was not used in the screening.

Owing to these conditions, the actual figures for patients must be somewhat higher than those revealed in the present study, and this must be considered when conclusions are drawn from the results obtained.

The irregular antibodies may be of importance in relation to pregnancy and blood transfusions.

The problems in relation to *pregnancy* are fairly simple. In the light of our present knowledge, blood-grouping and Rh determination are indicated in all pregnant women, and investigations for Rh antibodies must be considered a minimum requirement in all pregnant women who prove to be Rh:D-negative. If the obstetric history is suggestive of haemolytic disease in previously born infants or reveals that the patient has received multiple transfusions, special serological investigations are required, so that the possibility of haemolytic disease due to antigens other than Rh factors is excluded.

As far as *transfusions* are concerned, the conditions are far more complicated, and it is difficult to outline the minimum requirements.

We want to discuss the problems related to transfusions under two subheadings: (A) Rhesus antibodies, and (B) other irregular antibodies.

A. *Rhesus Antibodies.* — It appears from Table 3 that slightly less than 97 per cent of the Rh antibodies found were anti-D either alone or in

combination with one or more other Rh antibodies, which means that these 97 per cent of the Rh antibodies were found in Rh:D-negative persons. A little more than 3 per cent of the Rh antibodies were anti-C or anti-E, and these were all found in Rh:D-positive subjects. (This does not appear from Table 3.) From these figures it is seen that Rh:D-negative recipients are most liable to Rh complications, for which reason the following well-known prophylactic measures are taken: —

The recipients and donors are tested for the Rh:D-factor, and the Rh:D-negative donors are furthermore tested for the presence of Du-, C- and E-factors. The recipients are divided into:

Rh:D-negatives, who should be given D-negative, preferably cde/cde blood, and

Rh:D-positive, who may receive D-positive blood.

Obviously, provided that errors are not committed in the determinations, this procedure will with a reasonable amount of certainty eliminate the possibility of complications due to the 97 per cent of the Rh antibodies, since these antibodies were anti-D (possibly, plus anti-C and/or anti-E) present in the D-negative recipients, who will then only be given D-negative (cde/cde) blood. However, the possibility of complications due to the slightly more than 3 per cent of Rh antibodies (anti-C, anti-E) in D-positive persons is not eliminated. In Grove-Rasmussen's unpublished material, these antibodies were present in 17 per cent of the sera containing Rh antibodies. To obviate this hazard, which according to our figures should be present in approximately one of each 4,000 transfusions, according to Grove-Rasmussen in one of each 1,200 transfusions, two possibilities are open. (a) The D-positive recipients may be subjected to a complete Rh genotype determination and blood be given in agreement with the result obtained, or (b) a compatibility test may be used, by which it is possible to detect these rare antibodies. The first possibility is excluded both for practical reasons and due to the lack of the test sera required, so that only the second possibility remains. The question as to compatibility tests will be discussed in greater detail below.

The figures in the present material show that when no regard is paid to the Rh type, there will be a possibility of complications due to the presence of an Rh antibody in 121 of 17,000 unselected transfusions, i. e., in 7 cases in 1,000 transfusions.

However, in this connection, it must be noted that the selected material from the State Maternity Hospital with a high frequency of Rh antibodies (2.5 per cent as compared with only 0.4 per cent in the remaining part of the material) must affect the entire material in an unfavourable direction as far as the risk of Rh complications is concerned. If the patients from the State Maternity Hospital are excluded, this will cause some change in the figures. There will then remain 55 Rh antibodies in 14,351 sera, which gives a risk of Rh complications in about 4 out of 1,000 transfusions. However, this frequency is lower than the actual figure, since this part of the material comprises nearly all the donors with a low frequency of irregular antibodies.

B. *Other Irregular Antibodies.* — These represent a heterogeneous collection, which makes it difficult to indicate definite precautions or simple serological methods for the avoidance of complications due to these antibodies. However, these antibodies are so frequent and many of them so "malignant" that they cannot at all be neglected. According to the figures disclosed — 98 among appoximately 17,000 specimens — one of these irregular antibodies will be present in about six of 1,000 unselected recipients. This obviously does not mean that complications will necessarily develop in these six individuals. Some of these antibodies will be "cold", presumably without effect in vivo, and the transfused blood must, of course, contain the antigen corresponding to the antibody in order to cause complications. The latter fact, in particular, will cause the actual number of complications less than 6 per thousand, which only indicates the possibility of complications.

How is it possible to reduce or eliminate this risk?

As in the presence of Rh antibodies, two possibilities are open: —

A. Both recipient and donor may be investigated with a view to all these various blood-group antigens, and the blood to be given should be "compatible" also within these systems. However, this is impracticable, for which reason the second possibility must be considered.

B. One or more compatibility tests which — with a reasonable amount of certainty — guarantee that the recognition of all these various antibodies may be carried out. It is, however, impossible to outline a single compatibility test which fulfils this requirement, because the various antibodies differ widely in their mode of action and therefore require different methods. The conditions are further complicated by the fact that the principal requirement of a compatibility tests is that it is capable of revealing incompatibility within the ABO-system, which undoubtedly is the blood-group system that is responsible for the gravest transfusion reactions. This must obviously be born in mind, even though these considerations are principally concerned with the irregular blood-group antibodies.

It is impossible to enter into details concerning the optimal serological methods for the various irregular antibodies. Suffice it to say that a satisfactory present-day method may be: (1) The usual compatibility test at room temperature between recipient's serum and a saline suspension

of donor's blood cells (major cross match)*), and (2) Coombs' indirect test between patient's serum and donor's blood cells, preferably supplemented by antibody screening at least as regards recipients with grave risks (see below).

The first method should be capable of revealing ABO imcompatibility and of disclosing some of the irregular antibodies which cause risks for the recipient, for example, the fairly common anti-Le^a, in addition to strong anti-P, anti-M and a few other antibodies which are active at room temperature and complete. On the other hand, this method will only in exceptional cases reveal Rh antibodies, anti-Kell, anti-Fy^a and other similar antibodies, which usually are inactive at room temperature and incomplete.

The incomplete antibodies will in most cases be revealed by the second method. As these are usually immune antibodies, which have been induced by preceding stimulation either by transfusion or pregnancy, we believe that it may be justified only to supplement the first method by Coombs' indirect test and preferably also by antibody screening in recipients exposed to grave risks, viz: —

1. Women who have been pregnant, particularly if their obstetric history gives suspicion of immunization, i. e., women who have had one or more (late) abortions or borne children with signs of haemolytic disease.

2. Recipients who have previously been transfused, particularly if they have received several transfusions, or if their past history reveals transfusion reactions.

3. Recipients with certain disorders of the blood, particularly haemolytic anaemias, including haemolytic disease of the newborn. In the last case, the compatibility test is best performed between the mother's serum and donor's blood cells (if the ABO groups of mother and child allow for this procedure).

The procedures outlined here will obviously not safeguard against all complications in transfusions, but they will reduce the possibility of complications due to the relatively frequent irregular antibodies. The possible presence of such antibodies must be borne in mind whenever a transfusion is prescribed. In view of this as well as other risks during transfusions, a patient should be transfused only on sound indications. In this connection it must be pointed out that according to comprehensive American investigations (6) one death must be expected in 1,000—3,000 transfusions — that is, one death caused directly by the transfusion (all possible complications included). A blood transfusion is thus scarcely so harmless as the majority of members of the medical profession seem to suppose.

Another risk inherent in transfusions, which cannot be prevented by antibody screening or compatibility tests, is the possibility of immunizing the recipient by a transfusion. This will generally not be followed by immediate complications, but is represents a delayed hazard, which may become acute in relation to subsequent transfusions, or in relation to pregnancy in which the immunization may give rise to haemolytic disease of the expected child. In this way, a single transfusion may forever incapacitate a woman from giving birth to a normal child. In this connection, we want especially to warn against using husband or children as donors to women.

Because of the relatively high frequency of irregular antibodies demonstrated in this material, which must, of course, be a minimum figure, we have begun screening for irregular antibodies on sera from laboratories which perform their own ABO grouping and Rh typing on the specimens.

This procedure may supplement the common simple methods of blood grouping and reduce the risk of transfusion reactions in the recipients, particularly in hospital departments where it is not possible to perform the extended and more complicated compatibility tests.

Actually we believe that the figures disclosed by the present investigations indicate that a screening for irregular antibodies should precede every not very urgent transfusion, at least as far as recipients exposed to grave risks are concerned (see above).

The irregular antibodies are but one of the many problems which are attached to "blood transfusions". These problems increase with the use of blood transfusions. In particular, the weight of responsibility will rest more and more heavily on the persons performing the serological work related to the transfusions, and this must be borne in mind in the planning of such work in the individual departments and hospitals. This serological work has a special character. There are no laboratory investigations in which the consequences of an erroneous method or of misinterpretation are more serious than in blood grouping or compatibility tests. Death may be the immediate consequence of such a mistake. The printed instructions for the performance of these tests are deceptively simple and give a false feeling of security. For this reason it must be required that these investigations are performed by experienced personnel, who are familiar with these investigations.

*) We do not believe that the minor cross match is of great importance when registered, thoroughly investigated donors without irregular antibodies are used.

SUMMARY

A brief survey is given of the various blood-group systems and the blood-group antibodies known at the present time.

The authors have studied sera from approximately 17,000 blood specimens for their content

of irregular blood-group antibodies (i. e., iso-antibodies other than ABO antibodies). Screening for the antibodies was carried out by means of two different saline suspensions of trypsin-modified test blood cells and one albumin suspension of untreated cells. Of the sera studied, 217, or 1.28 per cent, contained one or more irregular antibodies. The material was partially selected, but it was found that at least 1 per cent of the sera from unselected patients contained irregular antibodies. It is emphasized that this percentage is obviously a minimum figure.

Of the 217 sera containing antibodies, 121 contained one or more Rh antibodies (55.3 per cent of the irregular antibodies). Of the sera containing Rh antibodies, 117, or 97 per cent, revealed anti-D either alone or in combination with one or more other Rh-antibodies, particularly anti-C. The 96 sera which did not contain Rh antibodies revealed a total of 98 irregular antibodies. The large number of anti-Le^a (57, or 26 per cent of all the irregular antibodies) is a noteworthy feature.

The significance of the irregular antibodies in relation to pregnancy and, in particular, to blood transfusions is discussed. It will be possible to avoid most transfusion reactions due to Rh antibodies by determining the Rh:D type of recipients and donors. In addition, Rh:D-negative donors should be studied for the Rh factors D^u, C and E, and D-negative recipients should only be given Rh:D-negative (cde/cde) blood.

Transfusion reactions due to a minority of the Rh antibodies (especially anti-E and anti-C unaccompanied by anti-D) and to the other irregular antibodies can be avoided only by special precautions, principally extended compatibility tests. If risks of immunization can be ruled out, major cross matching at room temperature may suffice, whereas this compatibility test should be supplemented by Coombs' indirect test in recipients liable to such risks (i. e., women who have been pregnant, previously transfused recipients, and patients with certain disorders of the blood, particularly haemolytic anaemias). Screening for irregular antibodies will be a further safeguard for the recipient and should be carried out at least in patients liable to immunization risks and in the donors. Special measures to be taken in the presence of an irregular antibody are mentioned. It is emphasized how important it is that blood-grouping work in hospitals is carried out by experienced personnel.

References:

1) *Grove-Rasmussen, M.:* Personal Communication.
2) *Kissmeyer-Nielsen, F.:* Vox Sanguinis 1955, *5:* 102—103.
3) *Levine, Ph., E. A. Kock, R. T. MacGee* and *G. Hill:* Am. J. Clin. Path. 1954, *24:* 292—304.
4) *Levine, Ph.:* Personal Communication.
5) *Mollison, P. L., A. E. Mourant* and *R. R. Race:* The Rh Blood-Groups and their Clinical Effects. Medical Research Council, Memorandum no. 27, London 1952.
6) *Wiener, A. S., P. N. W. Grant, L. J. Unger* and *W. G. Workman:* J. A. M. A. 1953, *151:* 1435—1443.
7) *Vogel, P.:* Bulletin New York Acad. Med. 1954, *30:* 657—674.

THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS

By ERIK HENRIKSEN and FRITS NEUKIRCH

The prognosis of subacute bacterial endocarditis (s. b. e.) has decidedly improved since the introduction into therapy of antibiotic agents.

In the untreated cases the disease usually ends fatally. Some authors, however, report spontaneous remissions in up to 3 per cent of the cases (2, 6).

With the advent of the sulphonamides, which were used in the treatment of patients with s. b. e., the number of remissions in selected material rose to approximately 6 per cent (2, 6).

Later on, attempts were made to improve upon results by a concurrent employment of heparin intended to prevent the deposit of fibrin on the heart valves, or possibly to dissolve such deposits rendering the entrenched organisms accessible to the sulphonamides.

By employing this method of treatment, 11 per cent are reported to have been cured (2).

Combined treatment with sulphonamide and hyperthermy meant another little advance, 16 per cent of the patients being bacteriologically cured. Finally a combined treatment of sulphonamides and typhus fever vaccine is reported to have achieved a percentage of remission of 25.

It was not until the introduction into therapy of penicillin that the s. b. e. prognosis radically changed, and with the range of antibiotics at disposal at the present time, a bacteriological cure can be effected in 80—85 per cent of all cases.

So far, no complete unanimity exists as to the optimal dosage of the various antibiotics.

From the Blegdamshospital in Copenhagen.
Head: Professor *H. C. A. Lassen.*

Thereports on penicillin treatment of s. b. e., which appeared during the first years of penicillin therapy, were often influenced by the prohibitive price of penicillin and the substance being available only in small quantities, but now that penicillin has been obtainable in ample supply over a number of years, it should be possible to arrive at an optimal therapeutic dosage.

Herring and Davis state in 1948 (4) that a daily dose of penicillin of 500,000 i. u., as a rule, will prove to be efficient, but in order to secure a broad margin, a daily dosage of 2 mill. i. u. is recommended for a period of six weeks. These investigators have undertaken sensitivity determinations in vitro, but have found that results cannot always be translated into clinical practice.

Friedberg (2) recommends starting treatment with 1.2 mill. units of penicillin daily, which is reported to be a sufficient dose in 90 per cent of the cases. As soon as bacteriologic information is received stating the susceptibility to penicillin of the organism concerned, dosage is decreased or increased, as the case may be, always provided that the daily amount of penicillin should in no case go below 600,000 i. u., Friedberg recommends the employment of crystalline penicillin twice during twenty-four hours. In case the total dose during twenty-four hours is to exceed 5 mill. i. u., continuous intravenous infusion is recommended. Treatment should extend over a period of 5 weeks, increasing to 8 weeks, in case more than two months have elapsed previous to the making of the diagnosis. In those cases in which the diagnosis rests solely on the clinical symptoms, without the causative organism being isolated, it is recommended to start with an initial dose of penicillin of 1.2 mill. i. u. daily, dosage being doubled every fourth day until a twenty-four hour dose of 20 mill. i. u. is being attained. If this dose is also without effect, it is recommended to employ other antibiotics. (Dihydrostreptomycin combined perhaps with Aureomycin).

In England "The Penicillin Trial Committee of the Medical Research Council" has for a number of years under the management of Cates and Christie (1) carried on extensive investigations in order to establish the optimal dosage of penicillin in cases of s. b. e. At the commencement of these investigations it was proved that treatment with a penicillin dosage of 1 mill. i. u., for five days failed in 83 per cent of the cases. If instead 500,000 i. u., were adminitered for ten days, treatment proved abortive in only 50 per cent of the cases, while administration of 250,000 i. u., for twenty days reduced the frequency of relapses to 22 per cent. This was conclusive evidence that in respect to a total dosage of penicillin of 5 mill. i. u., the duration of treatment is of decisive importance.

Subsequent investigations confirmed that treatment with penicillin 100,000 u. daily was entirely inadequate. A daily dose of 250,000 i. u. for one month was more effective, but did not, however, parallel the effect of a dose of 500,000 i. u. daily. On the basis of this evidence the researchers have treated 71 formerly untreated patients suffering from s. b. e. with 500,000 i. u., daily for a period of one month. Fourten of these patients either suffered relapses or died from uncontrolled infection, in spite of the fact that only in two of the patients did the causative organism prove more than twice as resistant as the Oxford-Staphylococcus strain. Among 18 fresh cases of s. b. e. treated with penicillin 2 mill. i. u., daily for 42 days, there were no relapses and no patient died with an existing infection. This standard of dosage is therefore being recommended by these researchers.

Hamburger and Stein (3) reported in 1952 that the duration of treatment can be reduced when employing very high doses of penicillin. The investigators have treated 12 patients with s. b. e. caused by streptococcus viridans with sodiumbenzylpenicillin to which is added small quantities of procaine. Twenty-four hour dosage was 2 mill. i. u., every third hour for two weeks. Among the patients treated, 2 suffered a relapse within a month, but both recovered, however, on readministration of the drug. Two patients died two and six months, respectively, following treatment, the one from pulmonary embolism, the other from cardiac insufficiency, both having been ridded of the cansative agent. Ten patients were alive at a follow-up study eight to forty-seven months after terminations of treatment, eight living normal lives. One of the eight patients, however, received treatment with digitalis.

In 1951 Kane and Finn (5) assessed the value of Aureomycin, Chloromycetin and Neomycin. The material comprises 12 patients with s. b. e. The authors came to the conclusion that "penicillin is the antibiotic of choice" in the treatment of s. b. e., presumably be use penicillin possesses both a bacteriostatic as well as a bactericidal effect, while the broad-spectrum antibiotics have only a bacteriostatic effect, and their use is being compromised by dyspeptic disturbances. Spies and co-workers (8) recommend reserving the use of Aureomycin for the treatment of cases produced by penicillin-resistant organisms.

If Aureomycin is to be used, then preferrably in combination with other antibiotics.

MATERIAL

During the years 1946—54, 19 patients were treated in the "Blegdamshospital - Epidemic Hospital" under the diagnosis of subacute bacterial endocarditis. The series comprises 10 male and 9 female patients between 5—64 years of age. Six out of nineteen patients were admitted under

Table I.
The incidence of a number of symptoms likely to confirm the diagnosis of subacute bacterial endocarditis.

	Fever	Cardiac murmur	Bacteremia.	Anemia. Hb. < 80%	Increased S. R. > 50 m. m.	Embolic lesions	Microscopic hematuria	Meningismus	Palpable spleen	Total cases.
No bacteremia demonstrated	2	2		2	2	2	1	0	0	2
Non-hemolytic streptococcus	12	12	12	7	7	7	5	4	1	12
Staphylococcus aureus	4	2	4	3	2	1	0	0	0	4
Streptococcus faecalis	1	1	1	1	1	0	0	0	0	1
In total	19	17	17	13	12	10	6	4	1	19

the diagnosis of s. b. e., sepsis or the like. Of the remaining patients not less than five were admitted under diagnoses like meningitis, meningismus or poliomyelitis. One of the patients was admitted with an incompensated heart disease, and subsequently fell ill in the department with fever and bacteremia.

Nine patients were reported to have rheumatic fever, 2 had had congenital heart disease, whereas 17 patients upon admission to the "Blegdamshospital" had a cardiac murmur indicating an organic heart disease.

At the time of onset of the disease, 2 patients did not present any objective sign of heart disease nor was any history of such brought to light.

In the majority of cases, the diagnosis s. b. e. rests on the cardinal symptoms of this disease, i. e., long periods of fever and cardiac murmur, and as a rule anemia. Other symptoms confirming the diagnosis appeared with the frequency stated in Table I. However, it should be pointed out that 4 patients upon admission were stiff of neck and back; besides, one of them had a hemiparesis. In 3 of them there were signs of a subarachnoidal hemorrhage, in the fourth of a lymphocytic meningitis.

Most important in establishing the diagnosis of s. b. e. is the demonstration of bacteremia. However, the question remains, how long one is to wait for positive blood cultures in clinically obvious cases before instituting treatment.

Newmann et al. (7) in 1954 report that with the aid of efficient technique, positive cultures will be obtainable in one of the first four specimens in all cases in which bacteremia is capable of being demonstrated.

At the "Blegdamshospital" where blood samples are inoculated at bedside, and the cultures immediately placed in thermostat, we are able to confirm this experience.

In respect to 10 patients who had not been treated with antibiotics prior to admission to hospital, bacteremia was demonstrated in 7 patients on a first blood culture, in 2 on second culture, whereas in the last patient bacteremia could not be demonstrated in spite of 8 cultures. If the patients had been treated with antibiotics during the weeks immediately preceeding admission to hospital it might have proved difficult to isolate any bacteria.

In one patient bacteremia was only demonstrated on fifth culture. (See Table 2.). In some few cases, in which cultures do not succeed on venous blood, bacteremia can be demonstrated on arterial blood or bone marrow.

Table II.
The number of blood cultures necessary to demonstrate bacteremia.

	1 culture	2	3	4	5	Sterile growth. (8 cultures)
Number of patients treated	7	2				1
Antibiotics prior to admission	5		1	1	1	1
In total	12	2	1	1	1	2

For the purpose of treatment there is a sharp distinction between patients with non-hemolytic streptococci infections and other patients, as in the case of the former they are suffering from organisms highly susceptible to penicillin, which susceptibility does not materially alter during treatment. At the "Blegdamshospital" such patients have consequently been treated with the same amounts of penicillin as are used to fight other infections due to penicillin-sensitive organisms, i. e., 300—800,000 i. u. daily, in divided doses of 2—4. Treatment has only in a few cases been combined with sulphonamides or other antibiotics. (Table III).

From Table III it appears that 2 patients died. In the one, a hospital nurse, aged 55, non-hemolytic streptococci were isolated in cultures before death occurred (autopsy was not allowed). The other was a twenty-four year old female textile worker who present a clinical picture of cardiac insufficiency. On postmortem examination there was no bacteriologic evidence of any active infection. In 11 out of 12 patients infected

Table III.

The treatment of 12 patients with non-hemolytic streptococci and 2 patients in whom no bacteremia was demonstrated.

No. of Record. Sex Age	Organisms isolated	Penicillin in 1000 i. u.	Number of days	Other Antibiotics	Number of days	Temp. normal after - days	Positive blood cultures - days after instituted treatment	Bacteriologic results
8123/46 ♂ 22	Non-hemolytic streptococcus	100 × 3	42	0		5	none	cured
292/40 ♀ 22	" " "	100 × 4	21	0		2	none	cured
9147/47 ♂ 22	" " "	100 × 3	42	0		2	none	cured
2322/48 ♀ 55	" " "	100 × 3 200 × 3 3000 i. u. 500 × 6	12 4 12 25	Streptomycin g 1 × 3	9	not achieved	119	died
7467/48 ♀ 49	" " "	200 × 3	42	0		3	none	cured
7525/48 ♀ 5	" " "	200 × 3 100 × 3 200 × 3 100 × 6	3 3 11 45	Sulphadiazine g 0.75 × 6	33	34	none	cured
8054/48 ♀ 53	" " "	200 × 4	67	Sulphadiazine g 1 × 4	14	2	3 and 10	cured
4127/49 ♂ 61	" " "	200 × 2 100 × 2	43 3	Sulphadiazine g 1 × 6	8	3	none	cured
5493/49 ♀ 22	" " "	200 × 4 200 × 3 200 × 2	12 12 12	Sulphadiazine g 1 × 4	7	3	none	cured
7773/49 ♂ 12	" " "	100 × 3	42	0		2	none	cured
4931/51 ♀ 54	" " "	150 × 2 200 × 3	7 36	0		6	none	cured
3727/52 ♀ 24	" " "	300 × 2	48	0		6	none	died
3044/49 ♀ 12	Sterile growth (8 cultures)	100 × 4 200 × 4 200 × 3 200 × 2	4 38 7 9	Sulphadiazine g 0.5 × 4	9	21	none	cured
6429/48 ♂ 35	Sterile growth (8 cultures)	300 × 6	42	Sulphadiazine g 1.5 × 6 Sulphadiazine g 1.5 × 6	3 32	2	none	cured

with non-hemolytic streptococci, and in 2 in whom no bacteremia could be demonstrated, the same amounts of penicillin as are used in the treatment of scarlet fever, pneumococcal pneumonia, and other infections caused by penicillin-sensitive organisms, were effective in curing the

bacterial infection — a result which compares favourably with those previously reported.

Treatment of s. b. e. is far more arduous if the disease has been caused by organisms less sensitive to penicillin. In the present material there are 5 such cases, i. e., 4 patients with staphylococcus aureus infection and 1 patient with streptococcus faecalis infection. These patients have been treated with penicillin, often by doses of millions, and with one or more of the other antibiotics, selected partly on experience, partly on sensitivity determinations in vitro of the causative organisms. Besides the employment of penicillin in the treatment of s. b. e. caused by staphylococcus aureus, bacitracin has been regarded as the antibiotic of choice (doses 10—20,000 units every six hrs.). In spite of intensive and prolonged treatment, results are inferior in these patients as compared with patients suffering from a non-hemolytic streptococcus infection.

A brief mention will be made of the five patients.

1) A 38 year old man suffering from s. b. e. caused by staphylococcus aureus was for almost a year treated with often heroic doses of all available antibiotics. He was discharged from hospital with negative blood cultures, but with pronounced cardiac insufficiency. Seven months later he was re-admitted owing to a recurrence of the disease which a few days later terminated fatally.

2) A 55 year old man with cardiac insufficiency. Apparently he was infected with staphylococcus aureus during hospitalization. A few days of treatment terminated fatally.

3) A 16 year old American girl, infected with staphylococcus aureus, ran a high temperature and with incipient aortic insufficiency was taken by plane to the U. S. Her fate is unknown.

4) A 64 year old man infected with streptococcus faecalis. He had formerly been treated at other hospitals for the same disease. He was discharged upon request after a period of eleven days in hospital for further treatment at home. He died about a month later, still suffering from active infection.

5) A 28 year old woman infected with staphylococcus aureus was discharged as being cured. She is alive two-and-a-half years after discharge in good general well-being. She has been through a normal pregnancy and there is no evidence of cardiac insufficiency.

Among 19 patients admitted for subacute bacterial endocarditis, 13 were discharged as being bacteriologically cured. This confirms the efficiency of antibiotic treatment.

What is the fate in store for these patients, who have all been through lengthy periods of bacterial infections primarily involving the heart valves? In order to elucidate this question, information has been collected during the spring of 1955 regarding these 13 patients, and all surviving patients have been subject to an after-examination.

Results of this after-examination appear from Table IV.

As will be seen from Table IV only 10 patients are alive at the follow-up, and of these 2 (No. 4 and 5) are greatly disabled from incompensated aortic failure. No. 6 and 7 have likewise an aortic insufficiency, but so far may live almost normal lives. No. 8 is strongly disabled from a spastic hemiparesis, caused by an embolism. No. 9 now suffers from a marked mitral involvement, restricting her physical activity, but as yet there is no manifest insufficiency. 4 patients (No. 10—13) live normal lives.

Table IV

Results of follow-up study of 13 patients discharged as bacteriologically cured.

	No. of record	Age-Sex	Follow-up in months.	
1.	8054/48	♀ aged 53	1	Died at home after 1 month. Pulmonary embolism?
2.	8123/46	♂ aged 22	44	Died from cardiac insufficiency. Aortic insufficiency.
3.	292/47	♀ aged 22	80	Died from cardiac insufficiency. Cor pulmonale.
4.	9170/47	♂ aged 22	84	Alive with marked cardiac insufficiency. Aortic insufficiency
5.	6429/48	♂ aged 35	77	Alive with marked cardiac insufficiency. Aortic insufficiency
6.	7773/49	♂ aged 12	39	Aortic stenosis and insufficiency. Still compensated.
7.	3044/49	♀ aged 12	70	Aortic stenosis and insufficiency. Still compensated.
8.	5493/49	♀ aged 22	65	Congenital heart disease. No cardiac trouble. Spastic hemiparesis.
9.	4931/51	♀ aged 54	40	Mitral stenosis and insufficiency. Still compensated.
10.	7467/48	♂ aged 49	88	Asymptomatic apart from cardiac murmur.
11.	7525/48	♀ aged 5	75	Asymptomatic apart from cardiac murmur.
12.	4127/49	♂ aged 61	68	Asymptomatic apart from cardiac murmur.
13.	3930/52	♀ aged 28	30	Asymptomatic - doubtful cardiac murmur.

By comparison, N e w m a n n et al. (7) at a follow-up study with an observation period of from 6 months to 5 years, report that approximately 70 per cent of the patients suffering from s. b. e. can be bacteriologically cured. At the end of the aforesaid period of observation 1/3 of the patient had died from cardiac insufficiency, another 1/3 are alive with cardiac insufficiency, while only the remaining 1/3 live normal lives.

Reviewing the material at disposal, it can be said that with the range of antibiotics available at the present time, a majority of the patients with subacute bacterial endocarditis can be bacteriologically cured of their infections, but that a very high proportion of surviving patients will be the victims of cardiac insufficiency. For the individual patient it may be difficult to decide the extent to which the cardiac insufficiency is due to the underlying heart disease, and how much importance can be attached to the eradicated bacterial infection. The frequent appearance of aortic diseases in young people makes it probable that the bacterial endocarditis is primarily to blame, especially because the aortic valves are only rarely attacked by rheumatic fever.

It seems safe to assume that early diagnosis followed by adequate treatment will prove of decisive importance in curtailing valvular lesions.

SUMMARY

On the basis of available literature, the most commonly employed treatment of subacute bacterial endocarditis is reported. It is pointed out that most authors make use of large or even very large doses of penicillin. A material comprising 19 patients suffering from s. b. e. who have been admitted to the "Blegdamshospital" in Copenhagen is discussed. Twelve patients were infected with non-hemolytic streptococci, 4 with staphylococcus aureus, 1 with streptococcus faecalis. In 2 patients no organisms could be isolated. The non-hemolytic streptococci being very sensitive to penicillin, the patients have been treated with similar amounts of penicillin as those employed in case of other infections due to penicillin-sensitive organisms. Results: approximately 90 per cent have been bacteriologically cured.

At a follow-up study, with a length of follow-up of from 2½ to 7 years, it was stated that approximately ¼ of the patients only are capable of living normal lives.

References:

1) *Cates, J. E. & R. V. Christie:* Quart. J. Med. New Seria 1951, *20:* 93.
2) *Friedberg, Charles K.:* Med. Clin. North. Am. 1950, *34:* 769.
3) *Hamburger, M. & L. Stein:* J.A.M.A. 1952, *149:* 542.
4) *Herring, A. C. & W. M. Davies:* J.A.M.A. 1948, *138:* 726.
5) *Kane, L. W. & J. J. Finn:* New Engl. J. Med. 1951, *244:* 623.
6) *Lichtmann, S. S. & W .Biermann:* J.A.M.A. 1941, *116:* 286.
7) *Newmann, W. J. M. Torres & J. K. Guck:* Am. J. Med. 1954, *16:* 535
8) *Spies, N., N. F. Dowling, M. H. Lepper, C. K. Wolfe & E. R. Caldwell:* Arch. Int. Med. 195, *87:* 66.

TOBACCO CONSUMPTION IN DENMARK

I.

THE DANISH NATIONAL MORBIDITY SURVEY OF 1950
COMMUNICATION NO. 8

By HENRY HAMTOFT and MARIE LINDHARDT

At the medico-statistical investigation into the health status of the Danish population, carried out in the years 1951—54 under the title of "The Danish National Morbidity Survey of 1950", 100,000 adults in all parts of the country were questioned over a period of three years as to their state of health in the month immediately prior to the interview. These questions, which also comprised matters relating to housing, occupation, etc., were the same throughout the three years.

In addition, however, the Committee secured information as to various other matters likely to be connected in one way or another with a person's health, the procedure being to devote brief periods to the asking of some special questions. For example, in the nine months from August 1952 to April 1953, inclusive, the interviewers inquired as to the persons' tobacco habits. After having answered the usual questions, the selected people were requested to supply information as to how much they smoked, the sheme being:

From the Committee on the Morbidity Survey. Chairman: *Johs. Frandsen.*

Do you smoke?

Yes.. How much do you normally smoke in a week? cigarettes about .. per week; cigarillos about .. " "; cigars about.. " "; pipe tobacco about g " "

No ..

The questions were readily answered, but in some cases with some surprise, as some were not always able to see the connection between the questions as to their health and those concerning the tobacco they smoked. Incidentally, a general evaluation of the quality of the answers shows that the actual consumption is rather higher than the figures communicated to the interviewers.

Before the analysis of the tobacco-consumption questionnaires had even started, the subject of the connection between the rapidly increasing mortality of pulmonary cancer and smoking, especially cigarettes, was raised by the medical profession. Statistical reports were first available from Denmark, the United Kingdom and the U. S. A., where the increase of pulmonary cancer mortality, especially among males, was very pronounced, and soon afterwards figures were published from other countries unequivocally pointing in the same direction: the higher the cigarette consumption, the higher the mortality from cancer of the lungs. The scintific conclusions provided occasions for lively and often temperamental debates in the press and elsewhere, and in many cases, at any rate temporarily, they seem to have influenced public opinion.

The Morbidity Survey Committee then thought it desirable to ascertain if there had been any change — which in this case means reduction — in tobacco consumption as a result of the public discussion, and therefore the closing four months of the survey period, January to April 1954, were utilized for procuring fresh information. This time the questions were:

Do you smoke?

Yes.. How much do you normally smoke in a week? cigarettes about .. per week; cigarillos about .. " "; cigars about.. " "; pipe tobacco about g " "

No ..

(If yes)
When did you begin to smoke regularly? .... or ....
(at least 5 cigarettes per week) age year

Do you inhale? Yes.. No..

Have you cut your smoking down since the public debate last autumn on tobacco and pulmonary cancer? Knew nothing about the debate.... No.... Yes....

(If yes)

What was your normal consumption of tobacco then? cigarettes about .. per week; cigarillos about .. " "; cigars about .. " "; pipe tobacco about g " "

In the present article we shall in broad outlines give an account of the smoking habits of the representative sample of the adult Danish population (15 years and over) in the two periods August 1952—April 1953 and January—April 1954. The statistical material has been treated in the same manner for both periods, though for the latter period we have certain information in greater detail which will be reported on in a subsequent article.

Table 1 is a survey of the smoking habits of males and females, shown separately according to age and the kind of tobacco. The results are presented graphically in Figs. 1—3. Before proceeding to an examination and appraisal the of

Table 1.
Survey of smokers and non-smokers by sex, age and form of tobacco. August 1952—April 1953 and January—April 1954.

	Sample size		Per cent of all interviewed						
MALES	total	of which smokers	all smokers	cigarette smokers	pipe smokers	cigar smokers	cigarillo smokers	all non-cigarette smokers	non smokers
Age									
15—19 years	880	537	61.0	28.3	32.5	—	0.2	32.7	39.0
20—29 "	1955	1613	82.5	35.1	45.0	1.0	1.4	47.4	17.5
30—39 "	2426	2058	84.8	31.6	42.1	4.2	6.9	53.3	15.2
40—49 "	2354	1952	82.9	26.6	37.0	7.4	12.0	56.4	17.1
50—59 "	1173	1400	79.0	15.6	34.2	13.6	15.5	63.3	21.0
60—69 "	1204	841	69.9	5.6	34.2	15.1	14.9	64.2	30.1
70 years and over	900	535	59.4	2.0	35.0	11.2	11.0	57.4	40.6
1952—53 total	11492	8936	77.8	23.4	38.2	7.1	9.0	54.4	22.2
1954	5453	4240	77.8	21.9	39.4	6.7	9.8	55.9	22.2
FEMALES									
Age									
15—19 years	838	343	40.9	40.0	0.5	0.1	0.4	1.0	59.1
20—29 "	2330	1370	58.8	57.3	0.7	0.1	0.8	1.6	41.2
30—39 "	2491	1257	50.5	46.8	0.6	0.2	2.9	3.7	49.5
40—49 "	2263	854	37.7	28.7	0.2	0.8	8.0	9.0	62.3
50—59 "	1756	548	31.2	16.8	0.1	1.2	13.1	14.4	68.8
60—69 "	1266	248	19.6	6.4	0.2	0.7	12.2	13.1	80.4
70 years and over	856	86	10.0	2.3	0.2	0.7	6.8	7.7	90.0
1952—53 total	11800	4706	39.9	32.9	0.4	0.5	6.1	7.0	60.1
1954	5273	2079	39.4	32.3	0.3	0.4	6.4	7.2	60.6

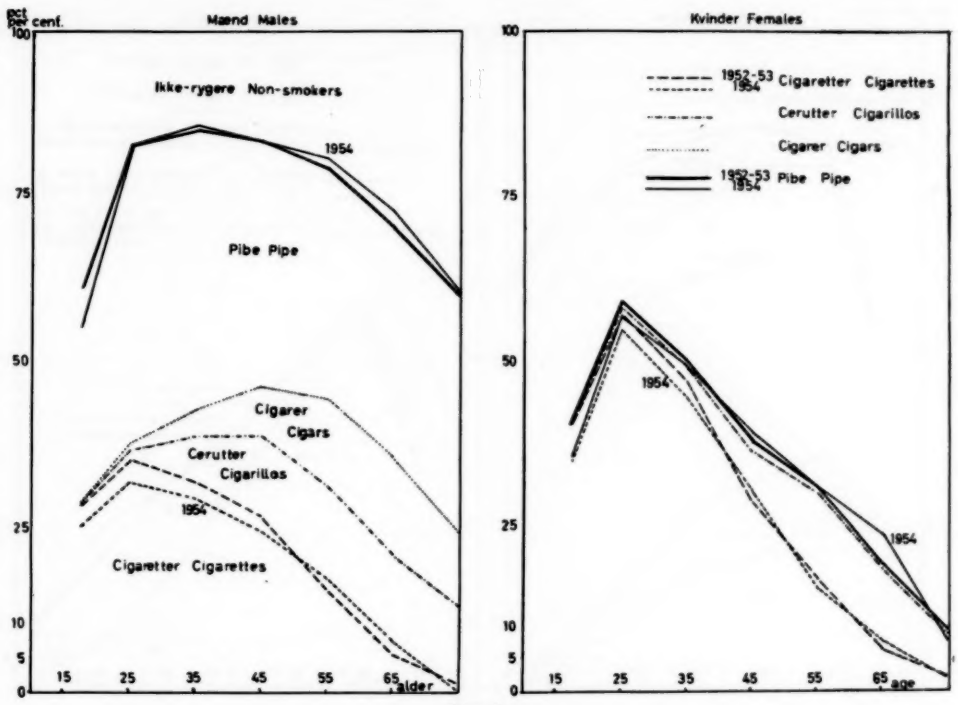

Fig. 1.
Smoking habits in Denmark by type of tobacco.
1952—53 and 1954.
Curves are from 1952—53 unless stated 1954.

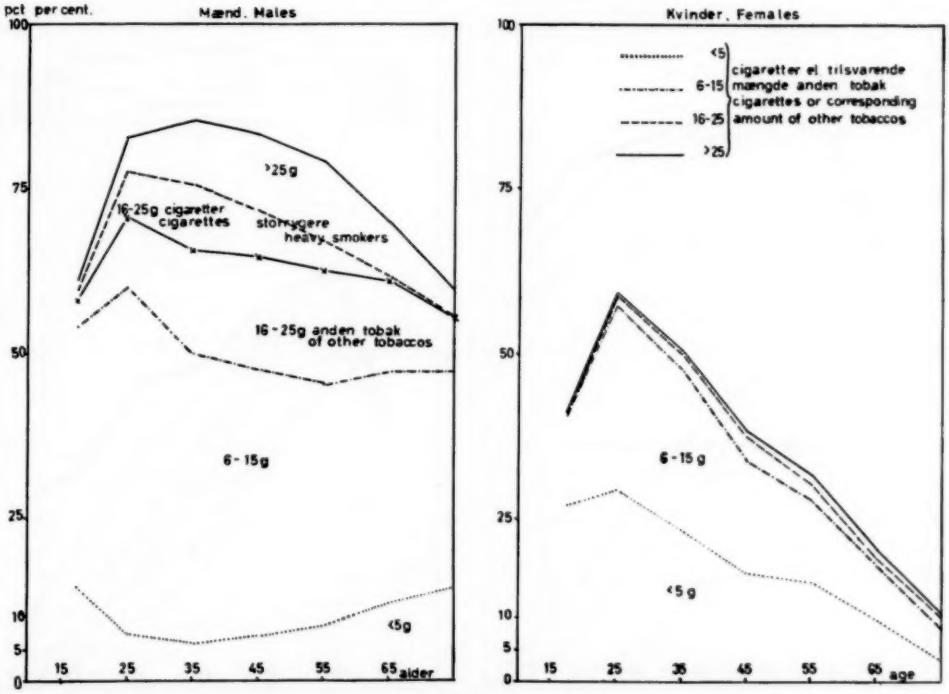

Fig. 2.
Consumption of tobacco in Denmark 1952—53 by amount of tobacco.

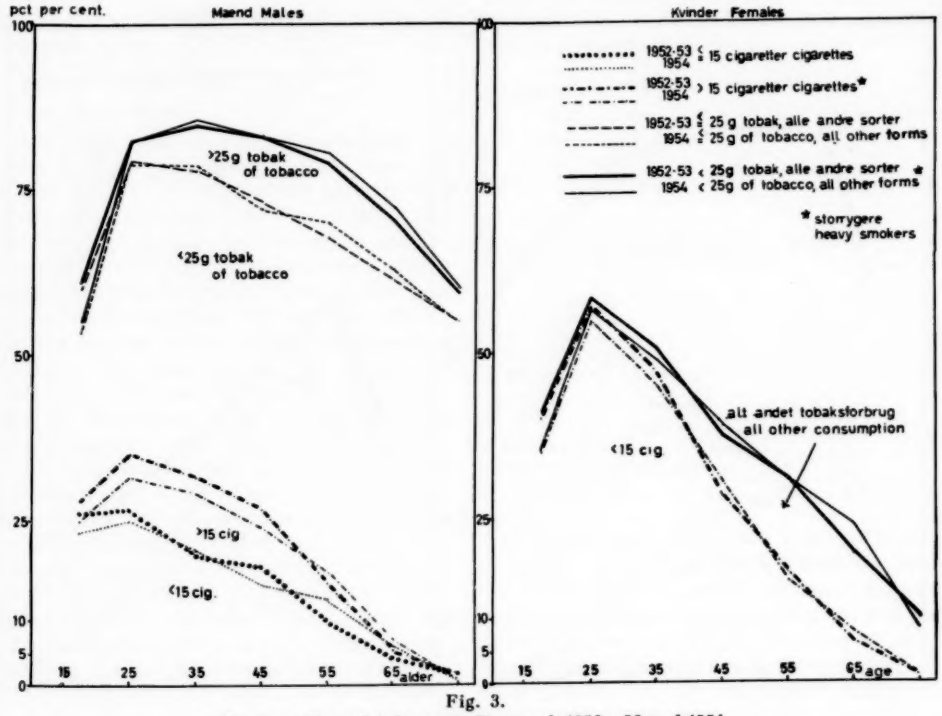

Fig. 3.

Consumption of tobacco in Denmark 1952—53 and 1954. Heavy smokers and others.

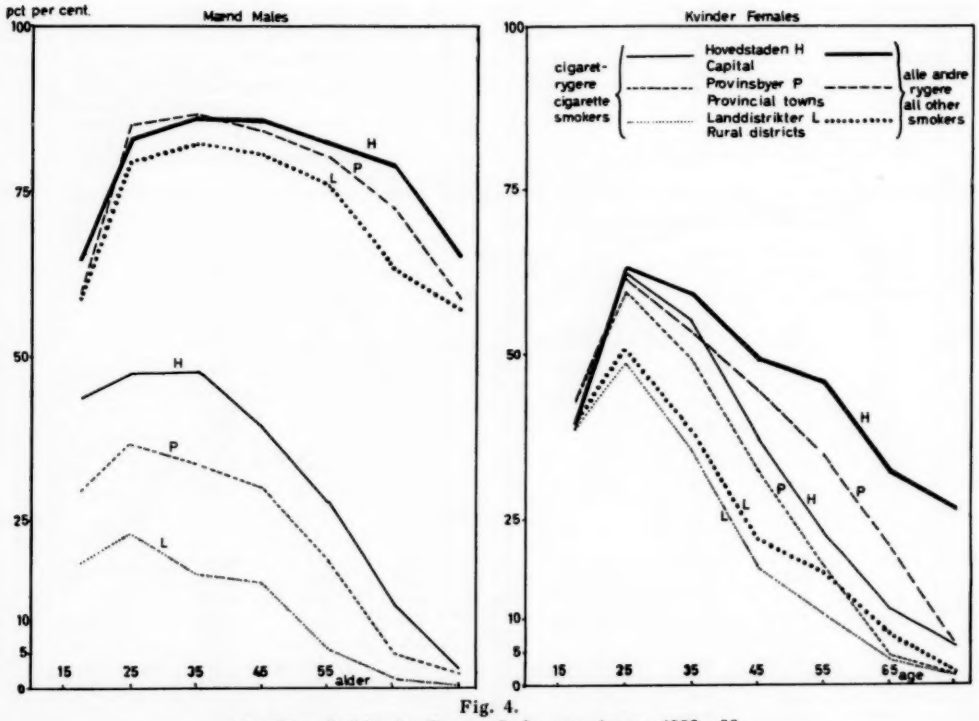

Fig. 4.

Smoking habits in Denmark by provinces. 1952—53.

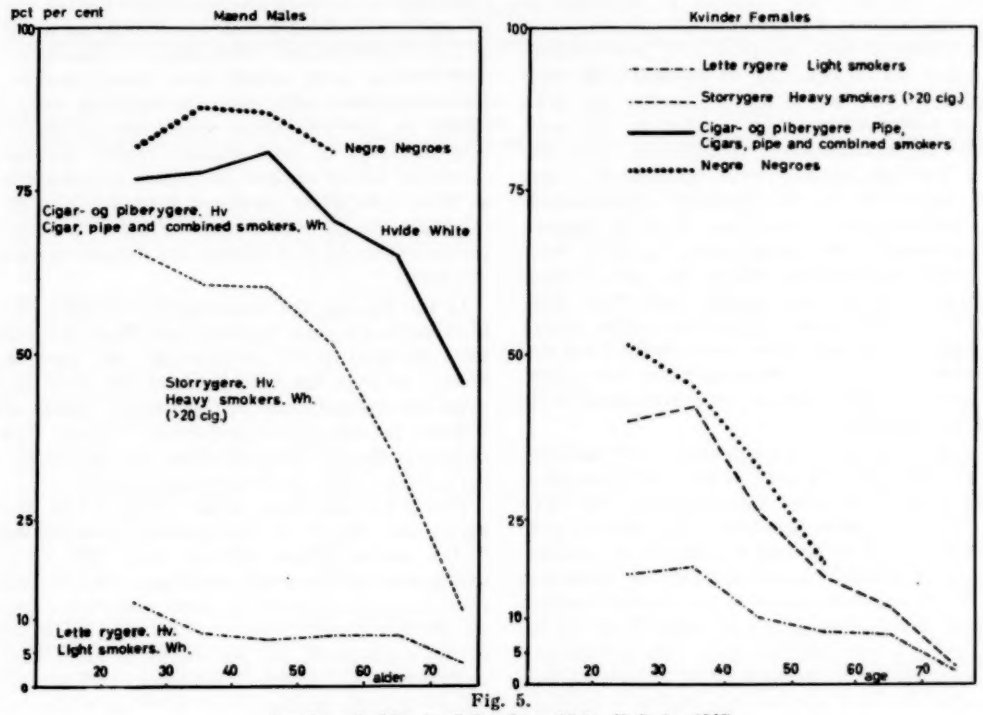

Fig. 5.
Smoking habits in Columbus, Ohio, U.S.A., 1947.

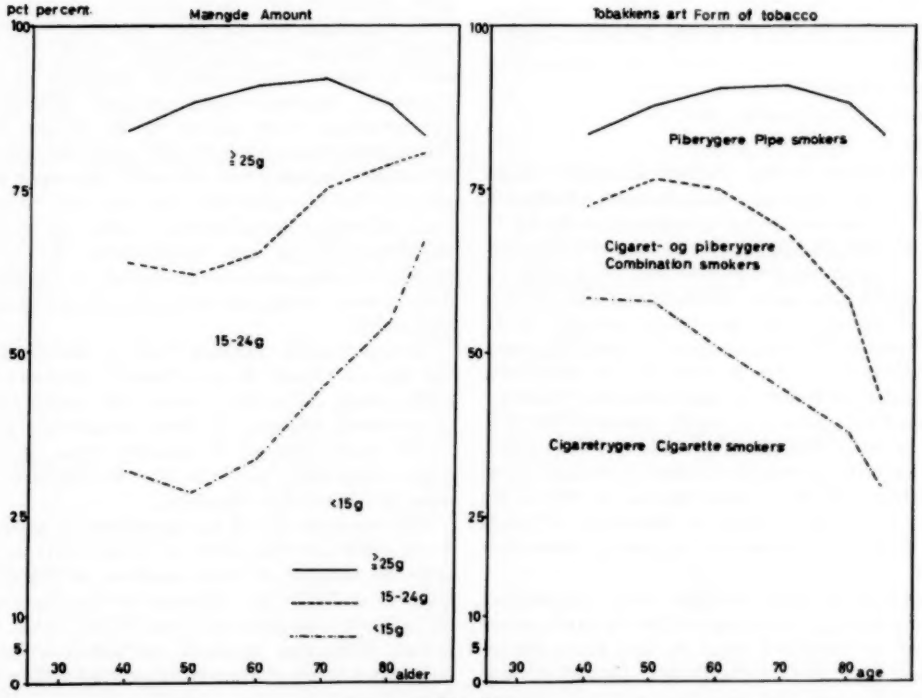

Fig. 6.
Smoking habits of male English doctors in 1951.

material, however, we consider it advisable to define the various groupings.

The division into smokers and non-smokers was made by designating as smokers all who admitted to smoking at all, whilst the few who did not state whether they smoked or not were counted as non-smokers. Subdivision into the group: cigarette smokers, pipe smokers, etc., was made according to the greatest consumption, those smoking more than one form of tobacco being placed in one group only, but then with their total comsumption. Where the consumption of different forms was equally high, they were classified in the order: cigarettes, pipe, cigars and cigarillos. Persons who were smokers but did not state the form of tobacco were, for males, reckoned as pipe smokers and for females as cigarette smokers.

Grouping the smokers according to the quantity smoked was carried out partly with reference to the tobacco-smoking investigations that have been made in other countries. The general rule was followed of reckoning a cigarette as containing 1 g, a cigarillo 4 g and a cigar 7 g. Thus one cigarette would correspond to 1 g of pipe tobacco.

When making comparisons with other countries, at any rate Anglo-Saxon, interest centres mainly upon the consumption of cigarettes. For Denmark we have divided the cigarette smokers into groups consuming:

1) Not more than 10 cigarettes a week (including a few persons whose consumption is not known.
2) More than 10 pr. week, but not more than 5 daily.
3) From 6 to 15 daily.
4) From 16 to 25 daily, and
5) Over 25 cigarettes per day.

Investigations in the United Kingdom make use of the same groups, with the sole difference that the borders are not drawn between 5 and 6, 15 and 16, but between 4 and 5, 14 and 15. In the present investigation we have not been able to follow quite the same subdivision, for purely technical reasons. In American surveys it is usual to reckon by the package of cigarettes, persons smoking up to one package (of 20) cigarettes a day being reckoned as light smokers, whereas those smoking more are heavy smokers. Having regard to American smoking habits (only about half a cigarette is consumed), the Danish criteria agree fairly well with those applied in the U. K. and the U. S. A., so that in Denmark a heavy smoker is one who consumes at least 15 cigarettes per day.

The picture is quite different when we turn to cigar and cigarillo smoking, which is much more prevalent in Denmark than in the Anglo-Saxon countries. The sizes of cigars and cigarillos vary considerably, and that also means their tobacco content, so there is no definite criterion as with cigarettes for a heavy smoker. Following the general rule and putting a cigarillo at 4 g and a cigar at 7 g of tobacco, one who smoker 3 cigars = 21 g of tobacco daily would be a heavy smoker if the comparison with cigarette smoking were to apply. As this evaluation would not be valid in this country, in the present report we have reckoned heavy smokers of cigars and cigarillos as those who daily smoke at least 4 cigars or 7 cigarillos. As to devotees of the pipe, those who consume over 25 g of tobacco are classed as heavy smokers.

In the figures, the shares of the various forms of tobacco are superimposed one above the other (by aggregating the percentages for each age group) so that the area between the lines indicates the consumption of the various forms, etc. Thus, the line drawn uppermost in each figure always indicates the total share (in per cent) of the smokers among all those questioned.

It will be seen from Table 1 that 77.8 % of all males and 39.9 % of the females were smokers in the period August 1952 to April 1953. Of the males, the largest total contingent, 38.2 %, were pipe smokers, followed by cigarettes 23.4, cigarillos 9.0 and cigars 7.1 %. 22.2 %, or a good fifth of the adult males, do not smoke at all. Females preponderantly smoke cigarettes, 32.9 %, then come cigarillo smokers, 6 % of those questioned. Three fifths of all adult females are non-smokers.

As might be expected, a smoker's age has a great deal to do with the form of tobacco he uses. Both cigarette and pipe smokers are relatively most numerous in the ages between 20 and 40 years, whereafter consumption moves distinctly over to cigars and cigarillos. Cigarette smoking especially decreases with the age, whereas the pipe-smoking habit seems to be rather firmly established throughout life, but with the aforesaid increased consumption between the ages of 20 and 40. The circumstance that the total consumption decreases considerably with age may be explained by the age distribution of cigarette smokers, as the other smokers even when they are over seventy years, do not reduce their consumption much.

Of the females, roughly half of those between the ages of 15 and 40 are cigarette smokers, relatively many more than among the males. On the other hand, females of these age-groups do not smoke much tobacco in another form, and it is only when they get into the forties that they acquire a taste for cigarillos.

The main results of the questions in January—April 1954 are also given in Table 1. It appears that the number of male smokers is exactly the same as in 1952—53, whereas for females there is an insignificant decrease, from 39.9 to 39.4. There is one difference, however, in that it is possible to discern some change in the consumption away from cigarettes — for males to pipe and cigarillo smoking; females, too, smoke fewer cigarettes and

Table II.

Smokers of cigarettes according to age, sex and amount of tobacco 1952—53 and 1954.

MALES	Smokers of cigarettes	Percentage of all interviewed smoking daily: less than 5 cigarettes	6—15 c.	16 - 25c.	more than 25 cigarettes	total
Age						
15—19 years	249	12.3	13.6	1.9	0.6	28.3
20—29 "	686	6.9	19.6	6.6	1.9	35.1
30—39 "	766	4.7	15.0	9.3	2.6	31.6
40—49 "	625	4.2	13.7	7.1	1.5	26.6
50—59 "	277	3.0	7.4	4.2	1.0	15.6
60—69 "	68	1.5	3.2	0.8	0.1	5.6
70 years and over	18	1.3	0.7	—	—	2.0
1952—53 total	2689	4.7	11.9	5.4	1.4	23.4
1954	1192	4.3	11.9	4.3	1.3	21.9
FEMALES						
Age						
15—19 years	335	26.5	13.0	0.4	0.1	40.0
20—29 "	1334	28.8	27.0	1.3	0.1	57.3
30—39 "	1166	22.5	22.6	1.6	0.1	46.8
40—49 "	650	15.1	12.4	1.1	0.1	28.7
50—59 "	295	11.4	4.8	0.6	0.0	16.8
60—69 "	81	5.0	1.3	0.1	—	6.4
70 years and over	20	2.0	0.2	0.1	—	2.3
1952—53 total	3881	17.6	14.3	0.9	0.1	32.9
1954	1701	17.1	14.1	0.9	0.1	32.3

rather more cigarillos. The changes are not great, but, they are unmistakable. See also Figs. 1 and 2.

The smoking intensity of cigarette smokers and other smokers appears from Table II and III respectively (and see Fig. 3). Applying the above criteria, 6.8 per cent of Danish males are heavy smokers of cigarettes, i. e., they have a daily consumption of more than 15 cigarettes. For the entire population of Denmark this corresponds to 110,000 males. The typical consumption is 6—15 cigarettes a day for 11.9 per cent of the males = 190,000 persons.

Among females the number of heavy smokers is quite minimal and comprises only 1 per cent of those questioned (corresponding to less than 20,000 females). 17.6 per cent of the female cigarette smokers consume fewer than 5 cigarettes every day, 14.3 per cent between 6 and 15. The decrease in the consumption of smoking referred to above is particularly applicable to the light smokers.

Heavy smokers of other tobacco than cigarettes in Denmark are defined above as consuming at least 25 g of tobacco daily. With this definition,

Table III.

Smokers of pipe, cigar and cigarillos according to age, sex and amount of tobacco 1952—53 and 1954.

MALES	Smokers of pipe, cigar and cigarillos	Percentage of all interviewed smoking daily: <1 cigar or 3 g of tobacco or 1 cigarillo on an average	1-2 cigars or 10 g of tobacco or 3 cigarillos on an average	3 cigars or 20 g of tobacco or 5 cigarillos on an average	4 or more cigars or over 25 g of tobacco or over 6 cigarillos on an av.	total
Age						
15—19 years	288	2.3	26.1	3.5	0.8	32.7
20—29 "	927	1.1	32.3	11.0	3.0	47.4
30—39 "	1292	1.8	28.7	15.7	7.1	53.3
40—49 "	1327	2.9	26.7	17.1	9.7	56.4
50—59 "	1123	5.6	29.6	17.0	11.2	63.3
60—69 "	773	10.3	32.0	13.6	8.3	64.2
70 years and over	517	12.9	32.7	7.8	4.1	57.4
1952—53 total	6247	4.3	29.5	13.6	7.0	54.4
1954	3048	4.3	30.8	13.4	7.3	55.9
FEMALES						
Age						
15—19 years	8	0.5	0.4	0.1	—	1.0
20—29 "	36	0.1	0.9	0.3	0.1	1.6
30—39 "	91	0.3	2.3	0.7	0.3	3.7
40—49 "	204	1.5	4.9	1.6	1.0	9.0
50—59 "	253	3.6	7.5	1.9	1.4	14.4
60—69 "	167	4.3	6.8	1.3	0.8	13.1
70 years and over	66	1.6	4.8	1.2	0.1	7.7
1952—53 total	825	1.5	3.8	1.0	0.6	7.0
1954	378	1.5	3.8	1.2	0.7	7.2